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Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia

By W B CASTLE (by invitation) and EDWIN A LOCKE, Boston, Mass

The action of liver in benefiting cases of pernicious anemia promptly and throughout the duration of the liver diet suggests the possibility of a deficiency etiology for the disease The deficiency would, however, seem not to be of the usual dietary type, for liver is ordinarily absent from the diet of unaffected normals The high incidence of a marked reduction of hydrochloric acid and pepsin in the stomach, sometimes discovered before the development of the disease, and not affected by the general improvement of the patient on a liver diet, suggests that the achylia may possibly play an intermediary rôle in causing the deficiency An obvious possibility, especially in view of the probable polypeptid nature of the effective principle in liver extract, is a deficiency of the gastric digestion of protein

To test this idea, the contents of the stomach of a normal man recovered one hour after a meal of 300 grams of rare Hamburg steak was administered daily to each of ten patients with pernicious anemia The material as obtained from the normal stomach was treated with strong hydrochloric acid to pH 2 to 3, incubated six hours, then neutralized with sodium hydroxide to pH 5, and given by stomach tube to the fasting patient In eight of the ten patients so treated clinical improvement, a characteristic rise of the reticulocytes and a progressive increase of the red blood cells was observed, comparable to effects ordinarily seen with small doses of liver in similar patients In one of the eight cases benefited the effect may have been initiated by a transfusion, and in one of the two cases showing no clinical improvement there was a slight increase in the reticulocytes at the expected time

The daily administration of mixtures of 300 grams of Hamburg steak with commercial pepsin or with 150 grams of the mucous membrane of the pig's stomach, incubated like the gastric contents, was found ineffective in three of these ten cases, and in two others In three cases of this series, and in two other cases 200 to 300 grams of Hamburg steak daily were given without effect In another case, mixtures of Hamburg steak and hydrochloric acid gave no benefit In view of Elders' work these controls must nevertheless be multiplied

At present a definite conclusion is impossible, but these observations suggest that the secretions of the normal gastric mucous membrane alone, or through their action on food proteins, can produce some substance capable on oral administra-

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The Effect of Hyperthyroidism on the Total Blood Count By HARRY BLOTNER, REGINALD FITZ, and WILLIAM P MURPHY, Boston, Mass

A few years ago Thompson showed that the plasma volume is diminished in myxedema We attempted to study the converse of his work by studying the plasma volume in hyperthyroidism We at once became interested in the behavior of the red cell count It appeared that the ordinary method for counting red cells is relatively inaccurate, the blood count is expressed in corpuscles per volume of blood without taking into consideration differences in total blood volume which may occur, or differences in individual body size and shape We made therefore, total red blood counts expressed in trillion red cells circulating per square meter of surface area When so expressed, patients with a low metabolic rate appear to have a low total red blood count which increases in almost direct proportion to an increasing metabolic rate Patients with hyperthyroidism have a high total red count The rising total red count which parallels a rising metabolic rate in thyroid disorders is very similar to the rising red count found in pernicious anemia cases under treatment with liver It appears, therefore, that the rate of metabolism may have an appreciable effect upon the total red count Our data bring to mind the possibility that the factor of stimulation of the metabolism of the blood forming tissues may be one possible factor in the beneficial effect of liver in pernicious anemia, although before this point can be particularly stressed, further observations are necessary

The Chloride, Base and Nitrogen Content of Gastric Juice After Histamine Stimulation By W SCOTT POLLAND and A M ROBERTS (by invitation) and A L BLOOMFIELD, San Francisco, Calif

See published article, JOUR CLIN INVEST, 1928, v, 611

Histologic Studies on the Small Peripheral Arteries and Arterioles in Ambulatory Cases of High Blood Pressure By J W KERNOHAN and E W ANDERSON (by invitation), and N M KEITH, Rochester, Minn

Tissues taken at autopsy from cases of malignant hypertension showed, as the significant histologic picture, a diffuse arteriolar lesion This suggested further study of the smaller vessels in tissue obtained from ambulatory patients with high blood pressure The biopsy material was obtained from the pectoral muscle The histologic study of the arterioles in this tissue form the basis of this report All cases show marked thickening of the walls of the smaller arteries and arterioles, especially hypertrophy of the muscular elements of the media and also hypertrophy of the internal elastic lamina Perivascular fibrosis is not constant There seem to be different degrees of hyperplasia of the lining endothelium of these vessels but the hyperplasia is not particularly constant in cases of malignant hypertension This finding agrees with that previously reported in autopsy cases An attempt has been made to relate the microscopic findings in these cases with the ophthalmoscopic examination of the retinal arteries, the appearance of the nail-fold capillaries and other clinical findings

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animals, urea has been substituted for nutritive nitrogenous foods In our experiments it has been added to an already adequate diet. Addis was unable to recover all the urea administered to normal individuals within 48 hours after it had been given, although the urea excretion had apparently returned to the normal level

If such large quantities of urea can be retained in the body without affecting the non-protein nitrogen of the blood, current theories which claim that urea is equally distributed throughout the fluids of the body, are untenable Furthermore, one should expect nitrogen thus retained to be swept out in subsequent periods if urea is, as has been generally believed, an obligatory waste end product of metabolism which must be excreted

Other studies aimed to determine more accurately the fate of urea are being undertaken

An Analysis of the Adrenalin Reaction and Its Relation to the Blood Chemistry etc By WILLIAM F PETERSEN, Chicago, Ill

The effect of adrenalin on the blood pressure has been studied in 100 so called normal individuals, as well as in some 75 patients and the results of the systolic blood pressure correlated with blood chemistry (calcium, potassium, phosphate, sugar, etc) as well as with the basal metabolism, the albumin-globulin ratio and the physical examination of the patient In addition, the reaction of the skin to pharmacological substances has been followed in the same patients The range of the reaction for the normal, as well as for the exaggerated reactions of the vagotonic and sympaticotonic individuals has been determined

Physiological Factors Influencing Inorganic Salt Secretion By RAY FARQUHARSON, and WILLIAM SALTER, (by invitation) and JOSEPH C AUB, Boston, Mass

Four patients were studied to determine the effects of exercise, change of diet and ingestion of acid and base upon their inorganic salt secretion

We determined the calcium, phosphorus and total base of urine and feces, the ammonia, titratable acid, chlorides, sulphates and nitrogen in the urine, and the serum calcium, phosphorus, carbon dioxide and protein The diet was then varied from a neutral to an acid diet and periods with alkalies, ammonium chloride and acid phosphates were given The effect of rest in bed was also studied

The results demonstrate the extent of physiological changes which may occur in the organism with respect to inorganic salt secretion The importance of such observations as a basis for the study of abnormal conditions is obvious

Pleural and Pulmonary Lesions in Rheumatic Fever By JOHN R PAUL, Philadelphia, Pa

The study reported below is essentially a pathological one based upon material from a series of 28 autopsies performed upon patients who died in the active stages of rheumatic fever The basis of selection of these cases was the

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early bronchopneumonia In spite of our negative bacteriological studies it may be relatively non-specific, representing a pneumonia occurring in a lung in which there is marked circulatory stasis, but its focal nature has suggested that it may be a purpuric manifestation

Frank early lobular pneumonia of proven bacterial origin has been a relatively uncommon finding in our series

A Study of Prolonged Auriculo-ventricular Conduction in Rheumatic Fever By ROBERT L LEVY and (by invitation) KENNETH B TURNER, New York City, N Y

A comparison has been made of the incidence of prolonged A-V conduction in rheumatic fever and in other diseases The material is taken from a general medical service during a ten year period The following points are made (1) prolonged A-V conduction is an important criterion in the recognition and differential diagnosis of rheumatic carditis, (2) prolonged conduction may afford evidence of the presence of myocardial lesions long after the clinical signs of rheumatic disease have subsided, (3) in four cases, prolonged conduction has been found during or shortly after an attack of acute tonsillitis, in the absence of other evidence of rheumatic infection, (4) in certain instances, there appears to be a definite relationship between variations in conduction time and salicylate medication In these cases, salicylate apparently exerts a favorable effect upon the lesions in the heart muscle

Observations on Goitre in Laboratory Rabbits By ALAN M CHESNEY, and (by invitation) BRUCE WEBSTER and THOMAS A CLAWSON

A high incidence of goitre has been observed in a series of 486 rabbits which were used for the study of experimental syphilis and have been under observation for varying intervals from September 1924 until the present time The frequency and extent of the condition have been such as to warrant the use of the term "endemic goiter" The animals were fed upon a standard diet of oats, cabbage and hay, and were not given water to drink The development of the goitre was not related to any particular breed of rabbits, but was definitely related to the time the animals had been caged It developed in non-syphilitic as well as in syphilitic rabbits

The enlargement of the gland was diffuse and involved isthmus as well as both lobes The glands were vascular and histologically showed marked hyperplasia with relative scarcity of colloid In a few, foci of lymphocytic infiltration were observed Many of the animals died in a cachectic state, without signs of terminal infection and in these the absence of body fat was striking

The heat production in the goitrous animals was found to be 16 per cent below that of "normal" rabbits on the average Some animals showed a rising metabolic rate prior to death The administration of Lugol's solution by mouth in doses of 1 minim per day was followed by a prompt rise in the metabolic rate,

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the injection of specific antipneumococcus serum in cases of lobar pneumonia due to Pneumococcus Type I, the serum was found to acquire these same properties A striking difference however, was observed between the spontaneously recovering and the treated cases in respect to the curve of the titer of pneumococcidal-promoting substances In the former cases the appearance of these bodies was followed promptly by recovery, in the latter the disease frequently persisted for some days in spite of the presence of a high concentration of immune substances in the serum This phenomenon is discussed

The Relation of the Hyperglycemia to the Renal Threshold in Older Diabetics and Its Clinical Significance By ALBERT A EPSTEIN, New York City, N Y

In the resting or fasting stage of the normal individual the blood sugar level is maintained by two factors, namely, sugar mobilization and sugar utilization After feeding, the sugar level rises and the curve which the hyperglycemia follows is small in amplitude and of short duration

In the resting stage of the diabetic the blood sugar level depends upon three factors, namely, sugar mobilization, suger utilization, and sugar excretion After feeding, the level of the blood sugar rises sharply and the hyperglycemia is of long duration

There is a distinct difference in the curves of the blood sugar levels of early and late diabetes This difference is ascribed to a change in the renal threshold for sugar The relation of the renal threshold to the blood sugar level is of two-fold character On the one hand, interference with the excretion of sugar (renal impermeability) causes a progressive rise in the blood sugar level, on the other, readjustment of the level of carbohydrate utilization in which the kidney participates (renal tolerance) leads to an elevation of the blood sugar which remains constant and represents a condition in which a balance between the rate of sugar mobilization and sugar utilization throughout the body has been established

The differences which early and late cases of diabetes show in their reaction to insulin with respect to the blood sugar level indicate that the persistent hyperglycemia in older or late diabetics is the result of a conservative process and represents an altered state in carbohydrate metabolism Recognition of this fact is important in the interpretation of the blood sugar findings in the different stages of diabetes and in the application of insulin in its therapy

On the Significance of the Respiratory Quotient after Carbohydrate Ingestion By WALTER R CAMPBELL and (by invitation) S SOSKIN, and E J MALTBY, Toronto, Canada

With the respiration calorimeter of Macleod we have confirmed on dogs the differences recently reported in the "respiratory quotient" after administration of glucose and dihydroxyacetone After administration of 25 grams glucose the respiratory quotient rises gradually to a maximum value of one, then gradually decreases, while after dihydroxyacetone it rises sharply to a maximal value often

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Metabolic Disturbances in White Snake Root Poisoning By H A BULGER and F M SMITH (by invitation) and D P BARR, St Louis

It is now well established that the disease known as "milk sick" is caused by the injection of milk from cows feeding on white snake root (*Eupatorium urticalifolium*) Preliminary experiments on animals poisoned by this plant have indicated that such studies present a new field for the investigation of ketosis and of fat and carbohydrate metabolism They also suggest the cause of certain clinical features of "milk sick" and indicate rational treatment of this mysterious malady We have found that it is ordinarily impossible to produce more than a slight ketosis in rabbits When poisoned with white snake root they developed a marked acetonemia and acetonuria Hypoglycemia was a prominent feature of the intoxication in these rabbits, most animals died with hypoglycemic convulsions Another prominent feature was a lipemia which may be extreme Glucose followed by a high carbohydrate diet apparently restored the animals to health The fatigue and rapid recurrence of symptoms following exertion in "milk sick," the coma and occasional convulsions suggest a relationship to hypoglycemia

The Isolation and Purification of a New Reducing Urinary Compound By HILDING BERGLUND and (by invitation) GRACE MEDES and ANNE LOHMANN, Minneapolis, Minn

The Circulation in the Pneumonic Lung as Studied by Means of Temperature Measurements during Diathermy By CARL A L BINGER, and (by invitation) RONALD V CHRISTIE, and WILHELM EHRICH, New York City, N Y

Previous studies have shown us that the lung of the normal dog can be heated only slightly (0 4°C) above the systemic temperature The cooling mechanism which dissipates the heat and prevents its localization in the lung was found to depend upon the pulmonary circulation rather than upon ingress and egress of air through the trachea and bronchi

In this study an experimental pneumonia was produced in dogs by the insufflation of pneumococci and of *B Friedlaenderi* The temperature of the consolidated and normal lobes was measured by thermocouples while high frequency currents were passed through the dogs' thoraces It was found that the pneumonic lobe was heated slightly (1° to 2°C) above the systemic temperature and the temperature of the normal lobes The change was of the same order of magnitude as seen in lungs with obstructed pulmonary arteries

The experimental data were correlated with the gross and histologic appearance of the lungs, which furnished an explanation for the heat retention on the basis of an impaired circulation This appeared to be due to the pressure of the intra-alveolar exudate which resulted in an ischemic state in which the alveolar capillaries were empty of blood The impairment of the circulation was further substantiated by post-mortem barium-gelatin injection preparations, which showed

Metabolic Disturbances in White Snake Root Poisoning By H A BULGER and F M SMITH (by invitation) and D P BARR, St Louis

It is now well established that the disease known as "milk sick" is caused by the injection of milk from cows feeding on white snake root (*Eupatorium urticaefolium*) Preliminary experiments on animals poisoned by this plant have indicated that such studies present a new field for the investigation of ketosis and of fat and carbohydrate metabolism They also suggest the cause of certain clinical features of "milk sick" and indicate rational treatment of this mysterious malady We have found that it is ordinarily impossible to produce more than a slight ketosis in rabbits When poisoned with white snake root they developed a marked acetonemia and acetonuria Hypoglycemia was a prominent feature of the intoxication in these rabbits, most animals died with hypoglycemic convulsions Another prominent feature was a lipemia which may be extreme Glucose followed by a high carbohydrate diet apparently restored the animals to health The fatigue and rapid recurrence of symptoms following exertion in "milk sick," the coma and occasional convulsions suggest a relationship to hypoglycemia

The Isolation and Purification of a New Reducing Urinary Compound By HILDING BERGLUND and (by invitation) GRACE MEDES and ANNE LOHMANN, Minneapolis, Minn

The Circulation in the Pneumonic Lung as Studied by Means of Temperature Measurements during Diathermy By CARL A L BINGER, and (by invitation) RONALD V CHRISTIE, and WILHELM EHRICH, New York City, N Y

Previous studies have shown us that the lung of the normal dog can be heated only slightly (0 4°C) above the systemic temperature The cooling mechanism which dissipates the heat and prevents its localization in the lung was found to depend upon the pulmonary circulation rather than upon ingress and egress of air through the trachea and bronchi

In this study an experimental pneumonia was produced in dogs by the insufflation of pneumococci and of *B Friedlaenderi* The temperature of the consolidated and normal lobes was measured by thermocouples while high frequency currents were passed through the dogs' thoraces It was found that the pneumonic lobe was heated slightly (1° to 2°C) above the systemic temperature and the temperature of the normal lobes The change was of the same order of magnitude as seen in lungs with obstructed pulmonary arteries

The experimental data were correlated with the gross and histologic appearance of the lungs, which furnished an explanation for the heat retention on the basis of an impaired circulation This appeared to be due to the pressure of the intra-alveolar exudate which resulted in an ischemic state in which the alveolar capillaries were empty of blood The impairment of the circulation was further substantiated by post-mortem barium-gelatin injection preparations, which showed

With the exception of three patients, the velocity of the pulmonary and of the nous blood flow after strophanthin or digitalis was either unchanged or in- :ased in all the patients with cardiovascular disease Although the average rdiac rate showed a reduction (10 per cent) the average velocity of pulmonary ood flow increased 35 per cent and that of the peripheral venous blood flow by per cent In all the patients in whom digitalis caused a definite improvement the clinical behavior, the velocity of blood flow was definitely increased The her three patients showed a slowing (20 per cent) of the pulmonary flow, with change in the velocity of the venous blood flow Proportionate to the slowing the pulmonary blood flow there was a reduction in the pulse rate

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ie Initial Effect of Moderate Undernutrition upon the Weight Curve in the Obese By MARK FALCON-LESSES, (by invitation) and L H NEWBURGH, Ann Arbor, Mich

The initial effect, upon the weight curve in the obese, of the shift from a main- nance diet to one of moderate undernutrition is the production of a tri-phasic rve The three phases occur as follows (1) The first phase is one of excessive :ight loss lasting from two to seven days (2) The second phase is one of weight aintenance and failure to lose weight, despite the sub maintenance calories— sting five to fifteen days (3) The third phase is one of excessive weight loss sting two or three days This tri-phasic curve does not occur if the caloric lue of the diet is excessively sub-maintenance but it has been produced in ery obese person so far studied

The first phase seems intimately connected with the katabolism of glycogen, ice it occurred when the subjects were in nitrogen balance and the weight losses :re much too great to be accounted for by the katabolism of fat

The second phase is one of hydration due to the retention of water as shown water-balance studies

The third phase is one of dehydration, apparently due to the loss of the excess iter stored up during the weight-holding period At the end of the third phase, e weight is exactly where it should be as calculated from the theoretical weight ss

he Rôle of Carbohydrate in Obesity With Special Reference to the Treatment of Obesity Complicated by Hypertension and Cardiac Disorders By BURGESS GORDON, and (by invitation) C W NISSLER, Philadelphia, Pa

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Experimental Leukocytosis and Leukopenia By PAUL REZNIKOFF, New York City, N Y

Recent investigations of Minot, Murphy and Cohn indicate that erythrocytic stimulation by chemical means is possible Doan and his coworkers have presented evidence that myelocytic stimulation may also be induced by nucleoproteins and nucleotides They obtained a preliminary leukopenia with nucleoprotein which they ascribed to the activity of the spleen but with nucleotides an immediate leukocytosis occurred

In the experiments reported here, nucleoprotein from liver and thymus (Dr John A Mandel), nucleic acid from yeast and thymus (Dr Mary V Buell, Dr P A Levene), and adenine sulphate and guanine hydrochloride (Mr Kenneth Blanchard, Dr Henry Jackson, Jr) were injected intravenously into rabbits When solutions of these substances in phosphate buffers were introduced, a leukopenia occurred, at first of the myelocytic forms and then, of the lymphocytes The myelocytic leukopenia was of short duration and was succeeded by a marked and sustained polynucleosis Increases in total cell count from 20,000 to 79,000 have been obtained with no apparent ill effects Solutions of phosphates caused a marked lymphocytic leukopenia This did not occur with NaCl or aqueous solutions containing no inorganic phosphate During the state of polynucleosis a marked shift to the left took place, indicating increased young cell formation or marked chemotaxis

The Development of the Ethyl Iodide Method for Determining the Cardiac Output of Man, a Test of the Method by Estimations of Flow through Dogs' Lungs Perfused at a Known Rate By ISAAC STARR, JR , and (by invitation) CLARENCE JAMES GAMBLE Philadelphia, Pa

In anesthetized dogs, the ethyl iodide content in mixed venous blood does not change materially during rebreathing The ethyl iodide content estimated from rebreathed air and the coefficient of distribution agrees with that found by analysis of mixed venous blood taken before rebreathing started The content in arterial blood agrees with the value calculated from alveolar air This permitted the measurement of flow by ethyl iodide while perfusing dogs' lungs at a known rate, satisfactory agreement resulting in five of six experiments

In normal persons breathing ethyl iodide the arterial content (by analysis) is correctly estimated from alveolar air collected automatically The ethyl iodide content in rebreathed air remains constant or falls very slowly during rebreathing for 1½ minutes, therefore we believe the content in mixed venous blood can be estimated as in dogs

The technique for the determination of blood flow in man is that of Henderson and Haggard, followed by rebreathing for thirty seconds, and determining the subject s distribution coefficient, (average normal blood = 6 1) Consecutive estimations on subject G reclining on three days = 3 9, 4 1, 4 0, 4 1, 4 0, 3 9, 3 9 On S (on three days) 5 3, 4 9, 4 1, 3 4, 4 6, 3.3, 3 0, 2 9, 3 5 liters per minute

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of fluids, accurate measurements of the vessels by micrometry and photography have been made It has been determined that the cerebral vessels may show changes in diameter consistent with mere passive expansion or collapse, following abrupt rise or fall in arterial pressure In addition, the arteries show changes exactly opposite in direction to these passive changes These can be brought about by stimulation of constrictor or dilator nerves, and by alteration of the chemical and physical (osmotic tension) constitution of the blood

It was concluded that the cerebral circulation is not altogether *passively* regulated, i e , from a distance by splanchnic or general systemic vasoconstriction and dilatation It is also dependent upon an active vasomotor mechanism for cerebral vessels, and by changes in the physical and chemical characteristics of the blood

In addition to vasomotor, osmotic tension and drug actions, other dilator mechanisms have been studied It has been determined that cerebral artery vasodilatation follows (1) reduction in the quantity of arterial blood circulating through the brain (severe hemorrhage, clamping the carotid arteries, circulatory failure and increased intracranial pressure), (2) reduction in the oxygen content of the arterial blood circulating through the brain (carbon monoxide), (3) increase in carbon dioxide content of the arterial blood circulating through the brain, (4) intravenous injection of acid or acid producing substances (lactic acid, acetone)

Hypothetically, these experimental changes in the quantity and quality of the blood create a physiological emergency They were always associated with cerebral vasodilatation

The Adaptation of the Circulation to Hyperthyroidism and to Hypothyroidism By HERMANN L BLUMGART and (by invitation) SAMUEL L GARGLE, Boston, Mass

The purpose of the investigation was to learn in what manner and to what degree the circulation of blood is accelerated to enable the transport of larger quantities of oxygen to the over-active tissues of thyrotoxic patients Ten thyrotoxic patients of different types have been studied The basal metabolic rates range from plus 11 to plus 50 per cent The speed of blood flow through the lungs was considerably faster than the average normal (10 8 seconds) in every patient studied In some patients the velocity of blood flow was more than twice the normal The velocity of venous blood flow from the arm to the heart was likewise greatly increased The extent of increase of the velocity of blood flow and of the basal metabolic rate were in general, proportional The vital capacity was reduced in all subjects even in the absence of any signs of congestive failure an observation in accord with other studies The conspicuous strain under which the heart labors even under basal conditions in maintaining such an increased velocity of blood flow is undoubtedly an important factor in causing frequent occurrence of heart failure in thyrotoxic states

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Effect of Some of the Purin-base Diuretics upon the Coronary Flow. By N. C. Gilbert and (by invitation) G. K. Fenn, Chicago, Ill.

Previous experimental work has shown the purin-base diuretics to have a vasodilator effect upon the coronary arteries, and to increase the coronary flow. This has not been completely confirmed by all investigators, and the objection has been made that the doses used were larger than the human therapeutic doses.

Because of the beneficial therapeutic results, further experimental work was done upon the intact animal. Under different methods of anesthesia a modified Morovitz cannula was inserted into the coronary sinus and the volume flow measured by means of a piston recorder tracing on a revolving drum. The doses used were low average human equivalents, and fractions of these. Theobromine sodium salicylate and acetate 0.01 gm. per kilogram, theocine sodium acetate 0.0032 gm. per kilogram, caffeine sodium benzoate 0.0066 gm. per kilogram and euphyllin 0.0014 gm. per kilogram. A definitely increased coronary flow was obtained with each of these, in the presence of a decreased systolic and diastolic pressure. Except when an extreme vasodilatation was already present, the increased coronary flow was apparently constant, with these drugs. In the case of the theobromine salts, the increased flow resulted in some cases with one-eighth of the above doses. In the case of euphyllin, theocine, and caffeine, results with less than one-half of the above doses were uncertain. The effect of anesthetics used on coronary flow was considered. Chloretone was shown to have an extreme vasodilator action.

Studies on Experimental Auricular Fibrillation Produced by Multiple Stimuli. By Arthur D. Hirschfelder, Minneapolis, Minn.

Auricular fibrillation can be produced in the exposed heart of the dog by stimulating either auricle with a single make and break shock thrown in rapid succession into three neighboring parts of the auricular wall. This is accomplished by means of three separate currents sent in rapid succession through four electrodes composed of blunt pointed copper wires about three millimeters apart, applied to the wall of the auricle.

The primary circuits to the three induction coils are made and broken by passing the current through a rapidly revolving drum covered with a perforated paper. As each perforation passes a spring wire which completes the circuit, the current is made and broken. Three perforations are located in an oblique row to insure sequence. A single cycle of three separate stimulations sets up circus movements which invariably produce auricular fibrillation. Fibrillation produced in this way often lasts much longer than that produced by ordinary faradization and frequently lasts from ten minutes to more than half an hour. Duration seems independent of cardiac weakness. Lasting fibrillation seemed to occur most commonly in slow hearts and in pilocarpinized animals. Stimuli to the auricle applied during sympathetic stimulation or after adrenalin following atropin, gave rise to fibrillation lasting only a few seconds. Further experiments are in progress.

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of myxedema showed no improvement with the liver treatment, studies of the blood were made following the use of dried thyroid gland, and the red blood count observed to return gradually to normal limits One patient with cancer of the prostate gland showed a striking increase in the reticulocytes and a rise in the erythrocyte count. It is entirely possible that this patient had cancer of the prostate gland and pernicious anemia In a second patient with cancer of the prostate gland there was no respone to liver therapy Two patients with leukemia showed no improvement. Liver was of no benefit in preventing the development of the anemia following the inoculation of patients with the malaria plasmodium for the treatment of general paresis

Whole Blood Immunity in Lobar Pneumonia By R L CECIL, and (by invitation) D R RHOADES, and W D SUTLIFF, Washington, D C

The pneumococcidal power of whole, uncoagulated blood has been measured The method in brief consists in determining the number of pneumococci which 0 5 cc of human blood will kill in 24 hours Heparin is the anticoagulant used

The number of pneumococci killed varied as follows

(a) In ward patients with minor complaints and without a history of lobar pneumonia from none to 10,000

(b) In patients convalescing from lobar pneumonia from 100,000 to 10,000,000

The following changes were observed in lobar pneumonia

1 In the acute stage pneumococcidal power is normal or less than normal

2 When bacteriemia is present before the crisis, no pneumococcidal power is present

3 Shortly before or at the time of crisis the pneumococcidal power of the whole blood becomes greater than normal

4 The pneumococcidal power of the whole blood reaches its highest point after the crisis

5 The simultaneous occurrence of bacteriemia (250 colonies of pneumococcus Type I per cubic centimeter of blood) and pneumococcidal power of high degree was encountered in a patient who developed acute pneumococcal endocarditis following Type I lobar pneumonia

6 Felton's antipneumococcus serum was administered to pneumonia patients with normal or subnormal pneumococcidal power Tests of these patient's blood made 24 hours after the injection of serum usually showed whole blood immunity fully as great as that found after spontaneous recovery from the disease

The Skin Temperature in Diabetes By HOWARD F ROOT, Boston, Mass

The temperature of the skin of 19 diabetics was determined by a method consisting of two copper constantan junctions, one located in a constant temperature bath—a Dewar flask—and the other applied to the skin The resulting current, which is measured on a galvanometer, is proportional to the difference in temperature between the two junctions

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previously reported studies of the effect of changes in acid-base relationships on epileptic seizures, permit a clearer analysis than has yet been possible of the physiological processes in the brain which contribute to seizures

Toxemia of Intestinal Obstruction, and Ileus Clinical Deductions Regarding its Nature and Treatment By CHARLES S McVICAR and (by invitation) JAMES F WEIR, Rochester, Minn

Inhibition of gastro-intestinal motility, whether due to organic or functional causes, is attended with grave consequences Death ensues if an organic obstruction persists and is equally a danger if functional inhibition is not relieved Animal experimentation has advanced knowledge with regard to this, and is directly responsible for the discovery that the toxic condition preceding death is associated with characteristic disturbances in the chemistry of the blood, namely nitrogen retention, alkalosis and hypochloremia Estimations of the chemical changes in the blood enable one to measure the severity of the toxemia and to estimate progress in treatment Animal experiments have as a rule been directed to the determination of the cause of death and while this is eminently desirable it is equally important that studies be made of earlier clinical manifestations and morbidity

It was observed that the toxic manifestations of motor inhibition were associated with diminished urinary output, and routine treatment now consists in maintaining adequate fluid intake to compensate for the loss of fluids by vomiting or by lavage of gastric contents It has been found that the intravenous route of administration is most satisfactory, since the oral route is precluded by vomiting, clysmata are soon rejected or lost because of incontinence, and subcutaneous administration is exceedingly uncomfortable if sufficient amounts are given For intravenous injection a solution is used containing 10 grams of sodium chloride and 100 grams of glucose to a liter of freshly distilled sterile water It was found that the intravenous administration of sodium chloride solution was not invariably followed by diuresis, and the glucose was added to insure urinary excretion

As clinical experience enlarged it became evident that cases could be grouped arbitrarily into (1) fatal cases with marked disturbances in the chemistry of the blood and anuria, at necropsy renal injury may be demonstrated, (2) severe toxemia also associated with marked changes in the chemistry of the blood and oliguria which, however, respond to intensive treatment and the patients recover without any discoverable evidence of renal injury, (3) mild toxemia with diminished urinary output and characteristic but moderate changes in the chemistry of the blood, the patients respond quickly to treatment, (4) clinical manifestations of motor inhibition, namely, vomiting and gastric retention with a low output of urine but without disturbance in the chemistry of the blood The last group is of special interest because if the earliest clinical manifestations of ileus may be recognized before changes occur it follows that the toxic syndrome is not due to a disturbance in the chemistry of the blood It was found, moreover, that in the

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This degree of new glucose formation has been observed in two patients The diet in each case was high in fat and low in protein and carbohydrate In one case, a diabetic of moderate severity, the process was stimulated by thyroid extract, and over a period of ten days the glucose excreted in the urine exceeded G by 128 grams In the other case, one of diabetes of ususual severity, insulin could be discontinued for only twenty-four hours while the patient was receiving such a diet During this period of twenty-four hours the glucose excretion exceeded G by amounts as great as 100 grams on two occasions Respiratory quotients were observed as low as 0 67

In both patients the observations were terminated by the development of extreme ketosis and acidosis, the carbon dioxide combining power falling to 19 or 20 volumes per cent The development of severe ketosis under these conditions suggests that these figures represent the maximum power of new glucose formation in diabetes mellitus

Hypoglycemic Reactions in a Diabetic without Insulin By HOWARD F WEST and BERTNARD SMITH, Los Angeles, Calif

This report concerns observations on the case of a boy who developed diabetes at the age of fourteen with coma He was seen first by the authors when in deep coma in April, 1924, one year after onset of diabetes The second period of coma was the result of discontinuing insulin and routine diet For the subsequent two years he ran a typical diabetic course, requiring from forty to fifty units of insulin per day while on a diet allowing 90 grams of carbohydrate per day with some variations in fat from time to time to avoid overweight In October, 1926, following acute ketosis (pre-coma) due to irregularities in diet and insulin, he developed sensitiveness to insulin which was discontinued For the following two months he was subject to severe and typical hypoglycemic shocks though the carbohydrate value of his diet was increased to 170 grams per day with supplementary feedings of carbohydrate food at times of severe reactions During this period his blood sugar varied from 19 mgm per hundred to 668 mgm in an entirely erratic and unpredictable manner

After a period of about three months he became stabilized and remained in good condition on a diet allowing 170 grams of carbohydrate without insulin In November, 1927, following an acute respiratory infection he again developed acute ketosis and glycosuria Insulin was again required for control After three weeks of treatment he again developed sensitiveness to insulin and for several weeks after insulin was discontinued he was subject to frequent hypoglycemic reactions with occasional periods of unconsciousness and convulsions in spite of high carbohydrate intake with frequent feedings He again became stabilized and is now in apparent good health and free from glycosuria on a diet allowing 180 grams of carbohydrate per day without insulin

The only significant physical findings during the hypoglycemic periods were an enlarged and tender liver, moderate edema and, on occasion, traces of bile in the urine

This degree of new glucose formation has been observed in two patients The diet in each case was high in fat and low in protein and carbohydrate In one case, a diabetic of moderate severity, the process was stimulated by thyroid extract, and over a period of ten days the glucose excreted in the urine exceeded G by 128 grams In the other case, one of diabetes of ususual severity, insulin could be discontinued for only twenty-four hours while the patient was receiving such a diet During this period of twenty-four hours the glucose excretion exceeded G by amounts as great as 100 grams on two occasions Respiratory quotients were observed as low as 0 67

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and calories-per-hour as compared to the probable values for persons of corresponding ages and heights, but of ideal weights This method of expression, we believe, depicts more accurately the pathological physiology of the obese

The initial data show an average weight of 222 pounds, 72 per cent above normal, and average surface 2 0 square meters, 26 per cent above normal The calories-per-hour average 71, giving an average basal metabolic rate of −2 0 per cent as usually calculated, but actually 23 per cent above the calories produced at normal weight Conversely, it may be stated that the increase in basal calories corresponds to the increase in surface (26 per cent) but not to that of weight (72 per cent) There is no evidence of a metabolic economy in obesity but rather an excessive energy exchange

After reduction, the average losses were 41 pounds and 0 17 square meters corresponding to a diminution of 47 per cent of the excess weight and 45 per cent of the excess surface The calories-per-hour average 61, a drop of 10 calories or 77 per cent of the excess energy Hence there is a definite decrease in energy exchange coincident with weight reduction The rate of change of calories is, however, over 1½ times as great as the rates of change of either weight or surface This evidence indicates again that body surface is not the sole regulator of metabolism

Observations on the Circulation of Guinea Pigs during Bronchospasm By F M SMITH and J S HARTER (by invitation) and H L ALEXANDER, St Louis, Mo

In order to determine the extent of filling of the heart during bronchospasm, the effective right auricular pressure was calculated

Method Large guinea pigs (650 to 1000 grams) were sensitized by intraperitoneal injections of egg white Under amytal anesthesia, cannulae were placed in the left carotid artery, in the right auricle (through the external jugular vein) and in the right pleural cavity Simultaneous pressures were recorded by tracings as were respiratory volumes Bronchospasm was then induced by intravenous injection of egg white and the circulatory response in relation to intrapleural pressure and depth of respiration noted

Results Unless bronchospasm comes on very suddenly there is a decreased filling of the right heart until asphyxia supervenes This is determined by plotting the algebraic difference between the mean right auricular pressure and the mean intrapleural pressure This gives the effective right auricular pressure which indicates degree of filling Sudden bronchospasm induces normal or increased filling

Serum Electrolytes in Infections and Nephritis By J H AUSTIN, and (by invitation) F WILLIAM SUNDERMAN and J G CAMACK

The serum electrolytes in infections and nephritis were studied in the same manner as previously reported in lobar pneumonia In lobar pneumonia, tuberculosis, chronic glomerular nephritis, and mercurial poisoning there was found a

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shown that the administration of salicylates is followed by an increased nitrogen excretion in the urine, but that this increase in nitrogen excretion is of a different type of nitrogen than that following iodides It was, therefore, decided to attempt a study of the reaction of patients suffering from various diseases to these drugs The patients were all on a constant protein diet with a constant water intake, taking due account of the water in the food In later experiments, the sulphur and phosphorus intake were also kept constant

In one case of "complete" myxedema there was no reaction after the ingestion of iodine This was to be expected from the previous experiments on dogs, in which a removal of the thyroid caused a disappearance of the urinary reaction to iodides There was a similar lack of response in a case of Addison's disease, but the results in this case are more doubtful, as the patient died a short time after the experiment

Of course, the chief interest in this connection is the study of nephritis So far, we have been able to study only two types, one, the hemorrhagic subacute type, in which there was a prolonged delay in the excretion of nitrogen after iodides, but in which the increased excretion of nitrogen after salicylates occurred promptly On the contrary, in a case which partakes somewhat of the character of nephrosis, there is a tendency to a reversal of this mechanism

The significance of these observations is not clear at present, but the indication seems to be that there is some fundamental disturbance in the nitrogen metabolism, not dependent upon the insufficiency of the kidney as a filter

Blood Volume Preceding and Following Splenectomy By H Z GIFFIN, GEORGE E BROWN, with technical assistance of GRACE M ROTH

This study was undertaken because of the fact that no data have been published on the spleen and splenectomy with relation to blood volume in man Observations were made on six cases of primary splenomegaly without anemia, eleven cases of hemolytic icterus, and eighteen cases of splenic anemia The Congo-red method was used to determine the blood and plasma volume

In fifty normal individuals, Brown, Rowntree and Roth, the mean values were as follows total blood volume 89 cc per kilogram, plasma volume 50 cc per kilogram, cell volume 39 cc per kilogram, and circulating hemoglobin 15 grams per kilogram

Primary splenomegaly without anemia showed a mean blood volume of 102 cc per kilogram, plasma volume 60 cc per kilogram, and a cell volume of 42 cc per kilogram,—a simply hypervolemia, suggesting the possibility that in primary splenomegaly without anemia the enlarged circulatory bed due to the splenomegaly and enlarged blood vessels necessitates a larger blood volume for circulatory needs

Hemolytic icterus before splenectomy showed a blood volume of 93 cc per kilogram, plasma volume of 74 cc per kilogram, and a cell volume of 19 cc per kilogram,—an oligocythemic normovolemia After splenectomy in hemolytic

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The Importance of Hematological Evidence in the Diagnosis of Pernicious Anemia By C P Howard, and (by invitation) E S Mills, Montreal, Canada

The authors have studied a series of 28 cases diagnosed as pernicious anemia at the Montreal General Hospital Only cases which were thoroughly investigated and subsequently followed, were accepted The object of the study was to test the reliability of hematological evidence

Twenty-three cases had a blood picture characteristic of the disease, while the remaining five were atypical in this respect, though classical in other ways When the latter group was subsequently followed the diagnosis in each instance was called into question Not one of these responded to liver treatment

A high color index, a large type of red cell, and a leucopenia with relative lymphocytosis, are constantly present in pernicious anemia In our experience cases which fail to show this blood picture are subsequently shown to be incorrectly diagnosed

There is a type of anemia occurring in young women which often begins during pregnancy and is refractory to ordinary treatment, which clinically resembles very closely true pernicious anemia, but has a distinct blood picture

Blood Groups among Maya Indians of Yucatan By W L Moss and (by invitation) James A Kennedy, Boston, Mass , and Rochester, New York

During the last decade considerable interest has been manifest in determining the percentage distribution among the four blood groups of the population in the various countries of the world

Geneticists have been active in collecting this data and have attempted to apply it to the investigations of racial origins and relationships

The bloods herein reported were collected during the summer of 1927 by Dr G E Williams, a member of the Carnegie Expedition to Yucatan

Blood for serum was collected in Wright's tubes and after coagulation, the serum was taken up in capillary tubes, the ends of which were sealed in the flame Blood for corpuscles was taken in a preserving fluid recommended by Rous and Turner (J Exper Med , 1916, xxiii, 219), consisting of a mixture of two parts of isotonic sodium citrate solution and five parts isotonic dextrose solution This mixture was put up in U-shaped tubes and after the introduction of one or two drops of blood the ends were sealed in the flame

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TABLE 1

Individual case analyses

Case number	Diagnosis	Date (1927)	Temperature	Pulse	Respiration	Total base			Cl	CO_2	Protein	Specific gravity	Non protein nitrogen	Calculated		
						Chemically determined	1 17 × corrected conductivity	Average						HCO_3'	B Pr (2 03 Pr)	Residual anions
			°F	*per minute*	*per minute*	*m Eq per liter*	*m Eq per liter*	*m Eq per liter*	*m Eq per liter*	*mM per liter*	*grams per 100 cc*	$\frac{20\ C}{20\ C}$	*mgm per 100 cc*	*m Eq per liter*	*m Eq per liter*	*m Eq per liter*
Normal values { Minimum						150	152	151	98	24	7 6	1 0260	18	23	15	4
Normal values { Maximum						164	162	163	108	33	8 8	1 0300	25	32	18	18
A 10	Tuberculous meningitis	March 15	100 2	98	30	144	146	145	92	25 1	8 6	1 0281	33 3	24	17	12
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		March 31	99 6	124	38	142	148	145	89	26 5	9 5	1 0317	53 7	25	19	12
A 13	Acute proliferative pulmonary tuberculosis	February 15	102 0	108	32	160	149	155	97	24 8	8 7	1 0320	37 7	24	18	16
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A 14	Miliary tuberculosis	April 26	102 8*	112	40	138	148	143	87	27 5	7 5	1 0256		26	15	15
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		February 22†				*147*	*136*	*142*	*90*	*21 1*	*6 7*	*1 0250*	*27 1*	*20*	*14*	*18*
A 16	Pleural effusion	March 31	99 0	80	26	147	153	150	94	27 4	7 8	1 0266	23 2	26	16	14
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MATERIAL AND METHODS

Thirty-three specimens of blood serum and two pleural fluids from twenty-nine patients on the Medical Services at the Pennsylvania Hospital and at the Hospital of the University of Pennsylvania in Philadelphia were examined

The technical methods used were those employed in our previous study (1926) Chemical determinations of total base by the method of Stadie and Ross have been compared further with conductivity determined with the Christiansen ionometer corrected by the formula of Gram and Cullen We find on further study the corrected conductivity times 1 17 equals in the average the total base chemically determined and we use this factor at present instead of 1 13 reported in our previous study

An approximate figure for the base bound by protein [B Pr] has been calculated by equation 54 of Hastings, Salvesen, Sendroy and Van Slyke (1927)

$$[B\ Pr] = 0\ 97\ [Pr]\ (pH - 5\ 26)$$

taking for pH, 7 35 Hence

$[B\ Pr]_{m\ Eq}$ is approximately $2\ 0\ [Pr]_{gms\ /100\ cc}$
$[HCO_3]_{m\ Eq}$ is taken as equal to $[CO_2]_{mM} - 1.3$
Residual anion $= [B] - ([Cl^-] + [HCO_3] + [B\ Pr])$

Protein was determined with the Abbe refractometer as in our previous study (1926) Specific gravity was determined at 20°C in a 2 cc pyknometer In graph 1 we have plotted all measurements of protein against specific gravity The correlation is fair

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Brief descriptions of each case studied are appended at the close of the paper The individual analyses are tabulated in table 1 Values outside of the normal range are in bold-faced type Groups of cases representing lobar pneumonia, tuberculosis and rheumatic fever are tabulated in table 2 showing the maximum, minimum and number of observations outside the normal range for each electrolyte in each group

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Renal

(Table 1, cases A 17 to A 22) The electrolyte distribution in two cases of acute nephritis (A 17 and A 21) differed from that in the pneumonia group in the fact that the reduction in chloride was compensated by an increase of one or more of the residual anions without any appreciable change in the total base This is similar to Atchley's observations with ligation of dogs' ureters On the other hand in our case of mercurial poisoning (A 19) with anuria for six days, two-thirds of the decrease in chloride and bicarbonate concen-

TABLE 3

Analyses of serum from mercurial poisoning case A 19

	Case A 19	Average normal	Difference
	m Eq per liter	*m Eq per liter*	*m.Eq per liter*
Total base (chemically determined)	146 5	154 7	−8 2
BCl	76 2	104 0	−27 8
$BHCO_3$*	22 2	25 8	−3 6
[$B_2HPO_4 + BH_2PO_4$]†	9 4	3 0	+6 4
B_2SO_4	12 0	1 0	+11 0
B Pr‡	18 0	16 0	+2 0
B organic acids§	8 4	4 9	+3 5
pH	7 31		
Non-protein nitrogen mgm per 100 cc	282 0		
Degrees depression in freezing point	0 63°C		

* $[BHCO_3] = [CO_2] - 1\ 27$

† $\frac{B_2HPO_4}{BH_2PO_4}$ at pH 7 31 $= \frac{77}{23} [PO_4] = 5\ 3$ mM/L, $[B_2HPO_4 + BH_2PO_4] = 9\ 4$ m Eq

‡ B Pr = 0 97 (Pr) (pH − 5 26) (Pr) = grams protein per 100 cc.

§ Calculated by difference

tration in the blood serum was accounted for as is shown in table 3 by increase in serum phosphate, sulphate and organic acid and one-third by decrease in the total base chemically determined [2] There occurred in this serum a marked discrepancy between total base chemically determined and the serum conductivity so that it would not be permissible to average the value by the two methods The cause for the discrepancy is not clear The relative rise in phosphate, sulphate and organic acid in the serum in this case with displacement

[2] This case has been presented from a somewhat different aspect by J M Hayman, Jr and J T Priestley, Am J Med Sci, 1928 (in press) The Importance of a Diuresis in the Treatment of Certain Cases of Mercuric Chloride Poisoning

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TABLE 3

Analyses of serum from mercurial poisoning case A 19

	Case A 19	Average normal	Difference
	m Eq per liter	*m Eq per liter*	*m.Eq per liter*
Total base (chemically determined)	146 5	154 7	−8 2
BCl	76 2	104 0	−27 8
$BHCO_3$*	22 2	25 8	−3 6
$[B_2HPO_4 + BH_2PO_4]$†	9 4	3 0	+6 4
B_2SO_4	12 0	1 0	+11 0
B Pr‡	18 0	16 0	+2 0
B organic acids§	8 4	4 9	+3 5
pH	7 31		
Non-protein nitrogen mgm per 100 cc	282 0		
Degrees depression in freezing point	0 63°C		

* $[BHCO_3] = [CO_2] - 1\ 27$

† $\frac{B_2HPO_4}{BH_2PO_4}$ at pH 7 31 $= \frac{77}{23}[PO_4] = 5\ 3$ mM/L, $[B_2HPO_4 + BH_2PO_4] = 9\ 4$ m Eq

‡ B Pr = 0 97 (Pr) (pH − 5 26) (Pr) = grams protein per 100 cc.

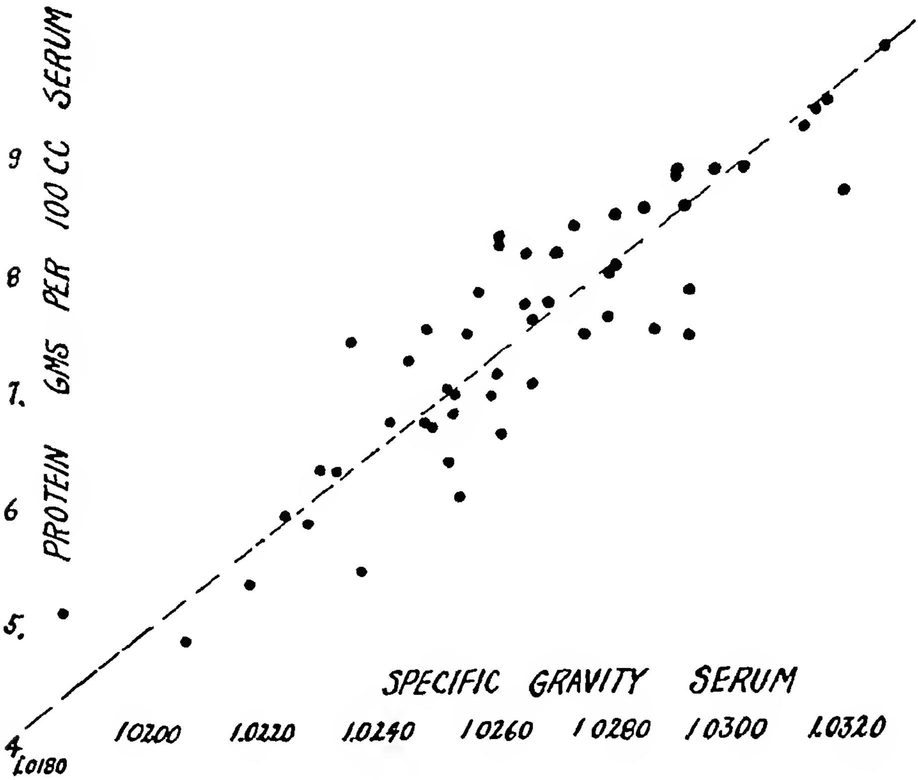
§ Calculated by difference

tration in the blood serum was accounted for as is shown in table 3 by increase in serum phosphate, sulphate and organic acid and one-third by decrease in the total base chemically determined [2] There occurred in this serum a marked discrepancy between total base chemically determined and the serum conductivity so that it would not be permissible to average the value by the two methods The cause for the discrepancy is not clear The relative rise in phosphate, sulphate and organic acid in the serum in this case with displacement

[2] This case has been presented from a somewhat different aspect by J M Hayman, Jr and J T Priestley, Am J Med Sci, 1928 (in press) The Importance of a Diuresis in the Treatment of Certain Cases of Mercuric Chloride Poisoning

Changes in CO_2 content

A recognizable though slight correlation between the concentration of CO_2 in the serum and the patients' temperatures is apparent in our cases as shown in graph 2 which includes also our cases of pneumonia It was found by Stadie, Austin and Robinson (1925) that,



GRAPH 1 PROTEIN REFRACTOMETRICALLY OF ALL SERA, AGAINST SPECIFIC GRAVITY

at either constant CO_2 tension or constant pH, an elevation of the temperature lowers the carbon dioxide capacity about 1 mM for every 4 6°F If the body temperature at the time when the blood was withdrawn in our cases be plotted as ordinate, and the CO_2 content be plotted as abscissae, it will be seen in graph 2 that the general trend of the CO_2 content was toward fall of CO_2 content with rise

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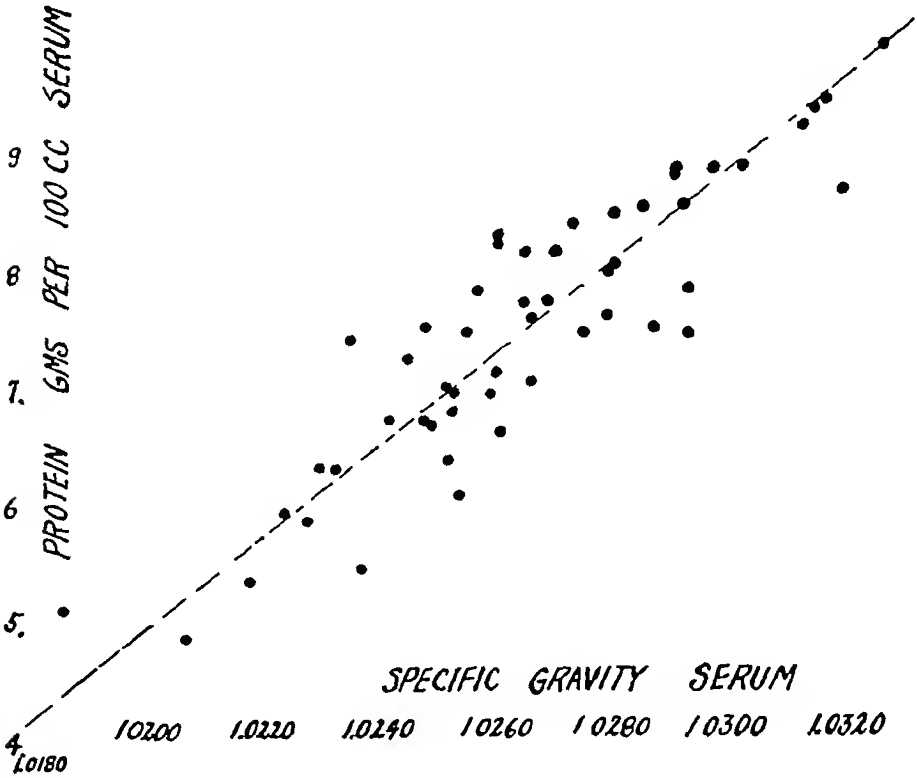

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Reduction in bicarbonate occurred in certain individuals but was not clearly characteristic of any of these groups

Reduction in refractive index was observed in the chronic glomerulonephritics A tendency to abnormal variations, sometimes high, sometimes low in refractive index was observed in the other pathologic cases

Elevation of the temperature was generally associated with a lowered CO_2 content This was greater than could be accounted for by the change in base bound by protein with change in temperature and must be attributed either to acidosis or to hyperpnea

The series as a whole and the case of mercurial poisoning in particular suggest the readiness with which chloride is reduced in the serum to make way for other anions

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Case A 16 (*1728*) Age 19, white male Admitted March 25, 1927 Left pleural effusion following a cold three weeks before admission Fluid aspirated four times in first week of hospitalization, a total of 2600 cc. A pure culture of *streptococcus hemolyticus* was obtained from the fluid, no tubercle bacilli were found Temperature 98 2 to 102 3, leucocyte count 10,000 to 34,000

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Case A 19 (*S-100*) Age 38, white, male Admitted to hospital May 22, 1927, and discharged July 4, 1927 On May 22nd the patient took five large bichloride of mercury tablets Twenty minutes later he was given milk and in one hour he had emesis after taking six raw eggs On admission to the hospital two hours after taking the poison, he was given gastric lavage At this time he had developed abdominal cramps and diarrhea The patient was completely anuric from the time of admission until May 28th during which time he received from 3 to 6 liters of fluid daily From May 28th to June 6th the urine output varied from 400 to 750 cc daily and contained a trace of albumin, occasional casts, and red blood cells From June 8th until the day he was discharged the urine output varied from 400 to 3750 cc averaging approximately 1200 cc and contained no casts, a trace of albumin and, after June 13th, sugar in traces Phthalein test on June 30th showed excretion of 1 per cent in two hours Edema of the face was observed on day of admission It became more marked and generalized on May 26th and had disappeared by June 2nd On Mav 24th the patient had convulsions and was irrational, becoming rational two days later The eye grounds showed no hemorrhages, exudates, nor choking of discs Daily blood urea nitrogen determinations increased steadily from 43 mgm per 100 cc. on May 23rd to 247 mgm on June 11th and then decreased gradually to 85 mgm on July 2nd

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It soon appeared that in the new situation there were difficulties which it was impossible to ignore Some of them it seemed possible to explore They are questions such as these Is the effect of digitalis in decreasing the volume output transient, as in Harrison and Leonard's dogs, or prolonged, as it appears to be in Burwell, Neighbors and Regen's patients, is it the same in animals with hearts of normal size and in animals the hearts of which are enlarged, does it make a difference whether the hearts are merely enlarged or does the presence of disease of the muscle also play a rôle in the final effect, does the presence of edema of the skin, tissues, and organs make a difference? If in all these situations digitalis behaves alike, is there perhaps a difference between dogs and man in the response to digitalis under any or all the heads which have been mentioned? And finally, in the interests of clearness, is the classification of digitalis as a depressant correct, and on which of its essential actions does the inference depend which places it in this category?

There is another matter of great interest which arises in connection with the studies of Harrison and Leonard It concerns the definition of beneficial action and how its presence is to be ascertained Shall beneficial action depend on the a priori assumption that it can be recognized and can be appraised in terms of one or another detailed effect of this drug, such as its effect on the blood pressure or the volume output or its effect on tone or on contraction or another of the many actions which it undoubtedly possesses? Or is it to depend on the net result of all these, on the general reaction of the whole man The matter is one really of great difficulty in connection with the circulation If digitalis, for instance, slowed the rate of the ventricles in auricular fibrillation but failed to relieve the patient permanently of whatever general disability affected him, would its use be continued even in the absence of a substitute? Examples like this may of course be multiplied This one is suggested to illustrate the point at issue, namely, whether beneficial action can without searching analysis be equated with any one of the details of the action of an agent, especially when it is scarcely known whether

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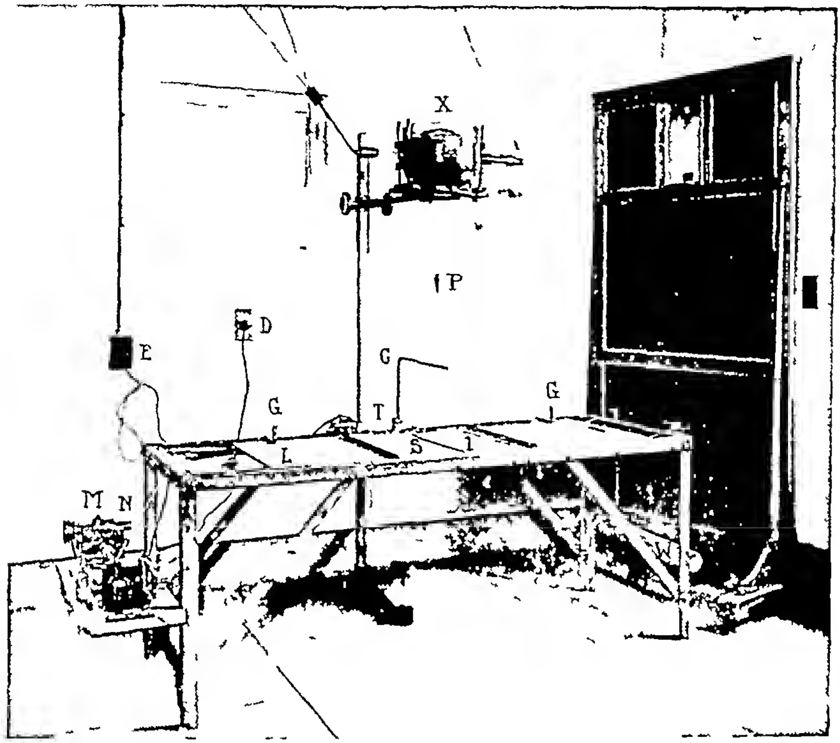

FIG 1 PHOTOGRAPH OF THE APPARATUS USED IN MAKING MOVING X-RAY PHOTOGRAPHS OF THE HEART

See figure 2 for a diagrammatic sketch of the apparatus *X*, x-ray tube 34 inches from control film, *P*, plumb line for centering x-ray tube over slit *S*, *C*, rod to indicate location of slit *S*, *T*, electromagnetic time marker from Petzold clock, *G*, guide for dog board, *D*, switch to Petzold clock, *E*, current switch to motor *M*, *L*, lead screen, *S*, 0 5 cm slit in the lead screen, *1*, guides for control film, *W*, counter-weight, *N*, cable for drawing moving film past the slit, *M*, motor

for human beings The photographic system instead of being vertical now functioned horizontally The dogs lay on a proper board This was placed upon a lead screen (fig 1 and 2, *L*) in which a transverse slit (fig 1 and 2, *S*) was cut 0 5 cm wide Opposite the slit near one end a time recording lever (fig 1, *T*)

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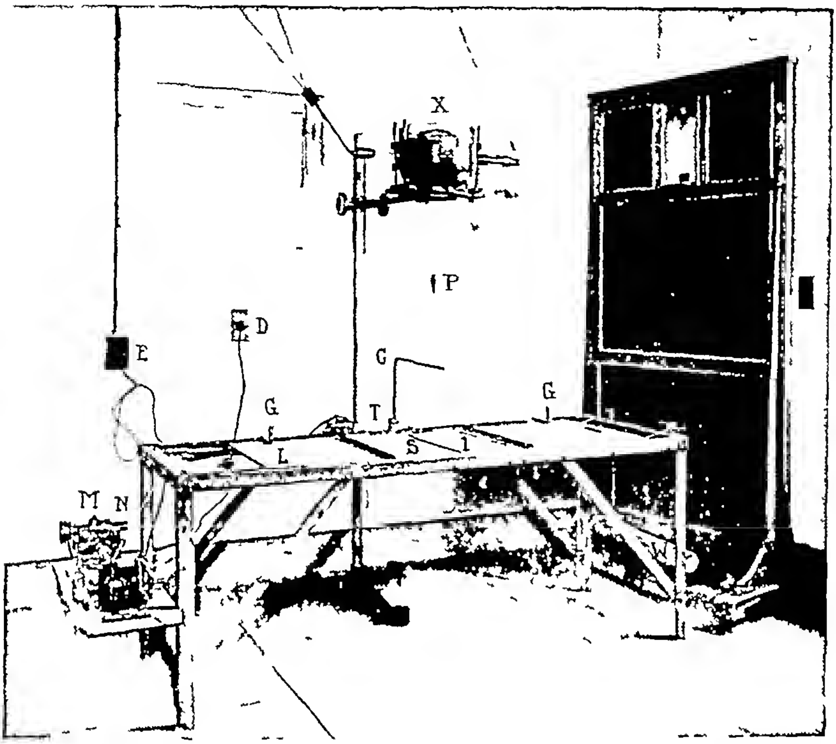

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Effect of digitalis on cardiac output, cardiac

Dog number and sex	Date	Weight	O₂ content: Arterial	O₂ content: Mixed venous	Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	O₂ capacity	O₂ saturation†: Arterial	O₂ saturation†: Mixed venous	Heart area‡	Heart area per cent of initial	Rib or intercostal space photographed
	1928	*kgm*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*volumes per cent*	*per cent*	*per cent*	*sq cm*	*per cent*	
257 Male	January 31	12 4	14 97	12 12	2 85	109	3 820	100 0	15 93	92 7	75 5	52 7	100 0	7th rib
			14 72	10 68	4 04	95	2 351	61 5	16 49	88 1	64 3	47 7	90 5	7th rib
	February 1	11 7	14 87	8 83	6 04	108	1 790	46 8	16 33	89 9	53 5	43 8	83 1	7th rib
	February 2	11 7	13 51	9 10	4 41	104	2 359	61 7	15 42	84 9	62 0	48 2	91 4	7th rib
	February 4	11 5	12 57	7 73	4 84	107	2 210	57 8	13 44	92 0	56 8	47 7	90 5	7th rib
	February 10	12 0	11 50	8 41	3 09	111	3 592	94 0	12 05	93 8	69 0	51 5	97 7	7th rib
258 Female	February 6	16 0	18 24	15 28	2 96	139	4 696	100 0	18 98	95 0	80 0	69 1	100 0	8th rib
			18 31	13 09	5 22	127	2 433	51 8	19 34	93 7	66 9	56 7	82 0	8th rib
	February 7	14 8	18 56	15 65	2 91	130	4 467	95 1	19 42	94 6	80 1	60 0	87 0	8th rib
	February 8	15 5	16 47	13 90	2 57	135	5 252	111 8	17 25	94 3	79 4			
	February 9	15 5	15 42	12 87	2 55	138	5 372	114 4	16 15	94 2	79 1	63 0	91 0	8th rib
259 Male	February 14	19 5	21 26	19 11	2 15	113	5 256	100 0	22 12	95 2	85 9	78 8	100 0	6th rib
			21 93	17 60	4 33	114	2 633	50 0	23 42	92 8	74 7	70 8	89 8	6th rib
	February 15	17 5	21 00	16 08	4 92	116	2 357	44 8	22 05	94 3	72 5	64 5	81 1	6th rib
	February 17	17 5	19 *32*	*15 90*	*3 42*	*125*	*3 655*	*69 5*	*19 98*	95 7	79 1	72 6	92 1	6th rib
	February 21	17 7	17 79	16 16	1 63	119	7 300	140 0	19 22	91 6	83 6	78 0	98 8	6th rib
261 Male	February 23	12 8	15 28	10 55	4 73	122	2 580	100 0	16 03	94 1	65 2	51 2	100 0	6th Inter space
			20 81	7 30	13 51	112	829	32 1	22 39	92 1	32 3	37 1	72 4	6th inter space
263 Male	February 28	10 9	21 38	15 58	5 80	99	1 707	100 0	23 63	90 5	59 7	56 2	100 0	7th rib
			23 88	14 36	9 52	86	902	52 8	25 50	92 9	55 9	51 1	90 9	7th rib
	February 29	10 3	21 55	15 96	5 59	95	1 698	99 6	21 93	97 7	72 3	50 4	89 7	7th rib
	March 2	10 7	18 55	14 84	3 71	96	2 588	151 5	19 16	95 7	80 3	54 4	96 8	7th rib
	March 8	10 8	17 72	14 02	3 70	97	2 622	153 5	18 26	95 9	76 2	57 4	100 2	7th rib
265 Male												6th LS / 6th rib	6th I S / 6th rib	
	March 5	9 8	16 24	14 01	2 23	96	4 *305*	100 0	17 *12*	93 7	81 3	39 8 / 40 2	100 0 / *100 0*	6th LS and 6th rib
			16 03	9 26	6 77	98	1 447	33 6	17 40	91 0	52 6	34 8 / 35 4	87 5 / 88 3	6th LS and 6th rib
	March 6	9 4	14 46	10 89	3 57	99	2 773	64 4	15 38	92 7	70 1	37 7	94 0	6th rib
	March 10	9 4	14 12	11 75	2 27	96	4 190	95 0	15 13	92 0	77 0	40 1 / 40 2	100 7 / 100 0	6th LS and 6th rib
266 Male	March 6	13 9	16 42	14 30	2 12	133	6 300	100 0	17 35	93 5	81 8	58 3	100 0	6th rib
	March 7	13 6	14 89	11 50	3 39	127	3 775	60 0	16 09	91 3	69 2	51 2	87 8	6th rib
	March 8	14 0	14 99	12 09	2 90	138	4 800	76 2	15 74	94 0	76 2	53 6	91 9	6th rib
	March 9	14 0	14 40	11 62	2 78	141	5 035	80 5	15 52	91 5	74 2	56 6	97 1	6th rib

* V = vomited.
† Before calculating the oxygen saturations 0.2 and 0 1 volumes per cent (the amounts of oxygen in physical solution) were subtracted from the arterial and mixed venous contents respectively
‡ These x ray photographs were taken at a distance of 34 inches
§ Tincture digitalis unless otherwise indicated I = intravenously M = by mouth.

Dog number and sex	Date	Weight	O2 content: Arterial	O2 content: Mixed venous	Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	O_2 capacity	O_2 saturation†: Arterial	O_2 saturation†: Mixed venous	Analysis of stationa…: Heart area‡		Heart area per cent of initial	
	1928	kgm	volumes per cent	volumes per cent	volumes per cent	cc per minute	cc	per cent	volumes per cent	per cent	per cent	sq cm		per cent	
257 Male	January 31	12 4	14 97	12 12	2 85	109	3 820	100 0	15 93	92 7	75 5	52 7		100 0	
			14 72	10 68	4 04	95	2 351	61 5	16 49	88 1	64 3	47 7		90 5	
	February 1	11 7	14 87	8 83	6 04	108	1 790	46 8	16 33	89 9	53 5	43 8		83 1	
	February 2	11 7	13 51	9 10	4 41	104	2 359	61 7	15 42	84 9	62 0	48 2		91 4	
	February 4	11 5	12 57	7 73	4 84	107	2 210	57 8	13 44	92 0	56 8	47 7		90 5	
	February 10	12 0	11 50	8 41	3 09	111	3 592	94 0	12 05	93 8	69 0	51 5		97 7	
258 Female	February 6	16 0	18 24	15 28	2 96	139	4 696	100 0	18 98	95 0	80 0	69 1		100 0	
			18 31	13 09	5 22	127	2 433	51 8	19 34	93 7	66 9	56 7		82 0	
	February 7	14 8	18 56	15 65	2 91	130	4 467	95 1	19 42	94 6	80 1	60 0		87 0	
	February 8	15 5	16 47	13 90	2 57	135	5 252	111 8	17 25	94 3	79 4				
	February 9	15 5	15 42	12 87	2 55	138	5 372	114 4	16 15	94 2	79 1	63 0		91 0	
259 Male	February 14	19 5	21 26	19 11	2 15	113	5 256	100 0	22 12	95 2	85 9	78 8		100 0	
			21 93	17 60	4 33	114	2 633	50 0	23 42	92 8	74 7	70 8		89 8	
	February 15	17 5	21 00	16 08	4 92	116	2 357	44 8	22 05	94 3	72 5	64 5		81 1	
	February 17	17 5	19 32	15 90	3 42	125	3 655	69 5	19 98	95 7	79 1	72 6		92 1	
	February 21	17 7	17 79	16 16	1 63	119	7 300	140 0	19 22	91 6	83 6	78 0		98 8	
261 Male	February 23	12 8	15 28	10 55	4 73	122	2 580	100 0	16 03	94 1	65 2	51 2		100 0	
			20 81	7 30	13 51	112	829	32 1	22 39	92 1	32 3	37 1		72 4	
263 Male	February 28	10 9	21 38	15 58	5 80	99	1 707	100 0	23 63	90 5	59 7	56 2		100 0	
			23 88	14 36	9 52	86	902	52 8	25 50	92 9	55 9	51 1		90 9	
	February 29	10 3	21 55	15 96	5 59	95	1 698	99 6	21 93	97 7	72 3	50 4		89 7	
	March 2	10 7	18 55	14 84	3 71	96	2 588	151 5	19 16	95 7	80 3	54 4		96 8	
	March 8	10 8	17 72	14 02	3 70	97	2 622	153 5	18 26	95 9	76 2	57 4		100 2	
												6th I S	6th rib	6th I S	6th rib
265 Male	March 5	9 8	16 24	14 01	2 23	96	4 305	100 0	17 12	93 7	81 3	39 8	40 2	100 0	100 0
			16 03	9 26	6 77	98	1 447	33 6	17 40	91 0	52 6	34 8	35 4	87 5	88 3
	March 6	9 4	14 46	10 89	3 57	99	2 773	64 4	15 38	92 7	70 1		37 7		94 0
	March 10	9 4	14 12	11 75	2 27	96	4 190	95 0	15 13	92 0	77 0	40 1	40 2	100 7	100 0
266 Male	March 6	13 9	16 42	14 30	2 12	133	6 300	100 0	17 35	93 5	81 8	58 3		100 0	
	March 7	13 6	14 89	11 50	3 39	127	3 775	60 0	16 09	91 3	69 2	51 2		87 8	
	March 8	14 0	14 99	12 09	2 90	138	4 800	76 2	15 74	94 0	76 2	53 6		91 9	
	March 9	14 0	14 40	11 62	2 78	141	5 035	80 5	15 52	91 5	74 2	56 6		97 1	

* V = vomited.

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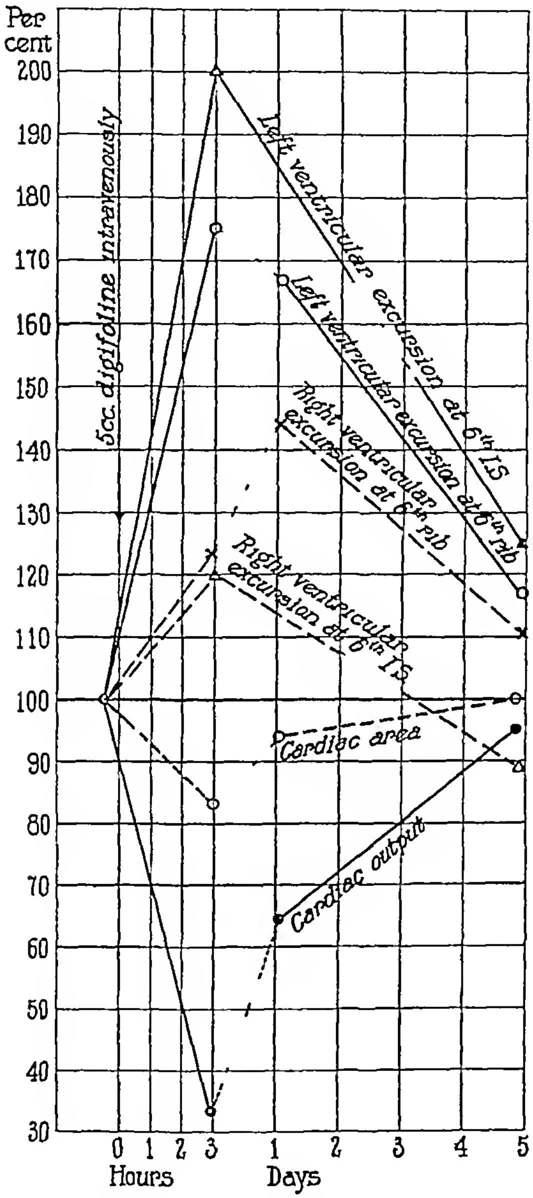

FIG 3 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 265

Photographs were made at the 6th interspace as well as at the level of the 6th rib As the effect of digitalis wore off cardiac output, cardiac size and extent of ventricular excursions returned simultaneously toward normal

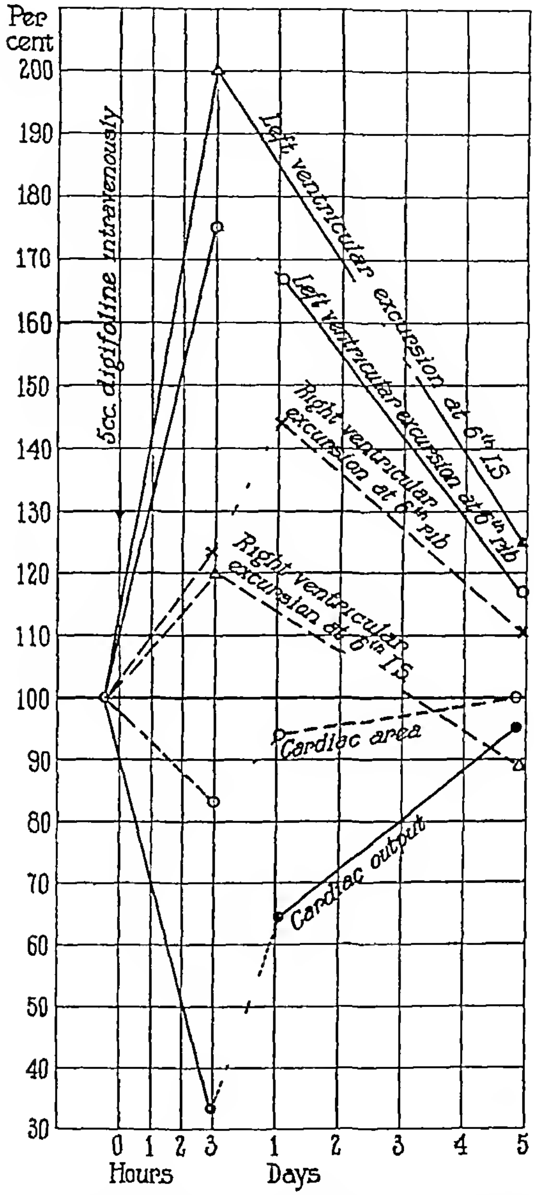

FIG 3 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 265

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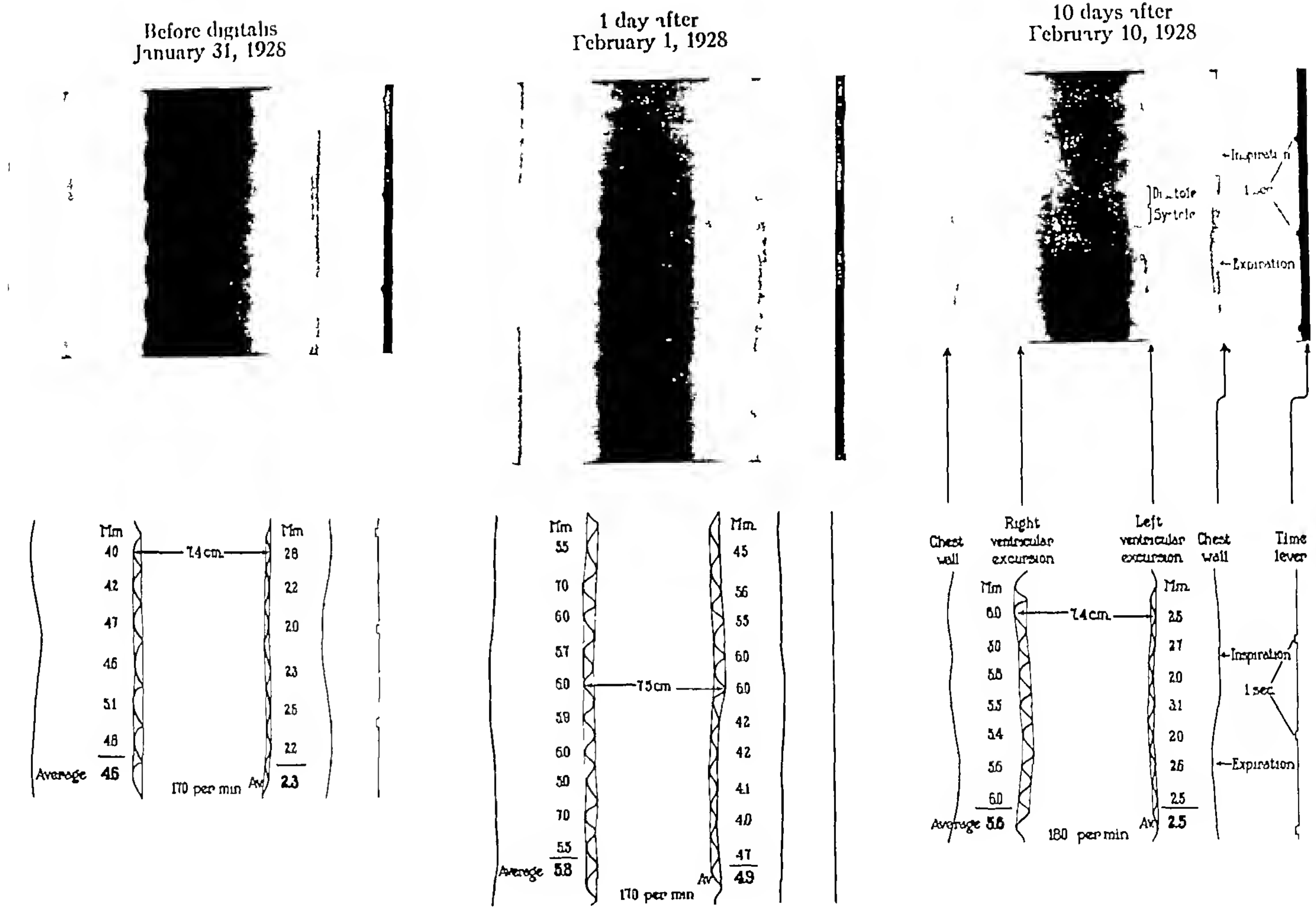
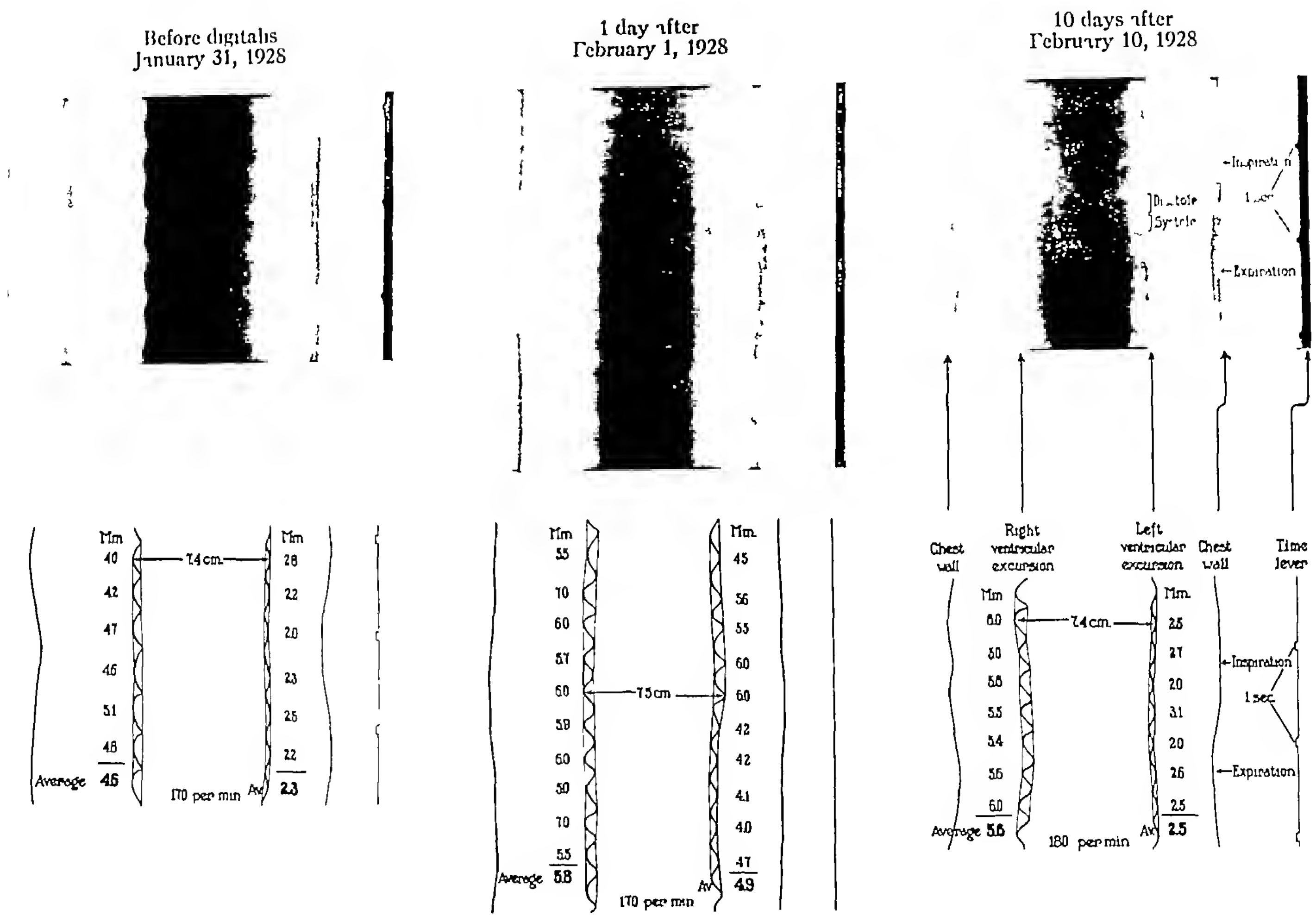


FIG 4 PHOTOGRAPHS OF THE MOVING FILMS OBTAINED AS DESCRIBED IN THE TEXT

Below each photograph is placed the corresponding tracing made from the original films of the excursions of the right and left ventricles respectively The photographs are reduced to one-fourth of their natural size



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Below each photograph is placed the corresponding tracing made from the original films of the excursions of the right and left ventricles respectively The photographs are reduced to one-fourth of their natural size

Cohn (Cohn) found that the dose for cats must be multiplied by the factor 1 16 to arrive at a comparable quantity for dogs We have accordingly injected this amount To several dogs we administered digitoline (Ciba) intravenously for the sake of comparison with the experiments of Harrison and Leonard (1926) Of this preparation we injected 0 5 cc per kilogram of body weight (Harrison and Leonard (1926), Pardee (1925)) To one dog we gave digitan (Merck) 1 0 gram by mouth The same phenomena resulted irrespective of the preparation that was administered

OBSERVATIONS

In 7 dogs we have complete data of the effect of giving digitalis on cardiac output, cardiac size and ventricular contraction (excursions)

The effect of digitalis on cardiac output In dog 257 the cardiac output was 3820 cc per minute (table 1, fig 5) Two and one-half hours after tincture of digitalis 2 8 cc had been given intravenously the output fell to 2351 cc per minute, there occurred, that is to say, a decrease to 61 2 per cent of the initial output Later, at 26½ hours, the output fell still further to 1790 cc, equal to 46 8 per cent only of the output at the beginning On the second day there was a change The output increased to 2359 cc and in 10 days returned to 3592 cc, that is to say, to 94 per cent of the initial value In this dog then there was after the administration of digitalis a decrease in cardiac output within 2½ hours which reached a maximum 24 hours later The return to normal, though not complete, took place at the end of 10 days

The results were similar in the other 6 dogs (table 1, figs 3 and 6), with this exception, namely that in 3 dogs (dog 258 (fig 6), dog 259 and dog 263) the output, following the initial decrease actually became greater than it had been at first This observation will be discussed later at greater length In general, though, the output decreased uniformly 2½ to 3 hours after the administration of digitalis, but the maximum was usually delayed until 24 hours later It varied between 34 and 62 per cent of the initial value (table 1) Later the cardiac output returned toward normal (dog 261, dog 265 (fig 3) and dog 266) or exceeded this value (dog 258 (fig 6), dog 259 and dog 263) The changes in output occurred irrespective of changes

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in heart rate (recorded electrocardiographically) though this was found usually to have decreased 2 to 3 hours after administration Later the rate returned to what it was at the outset of the experiment

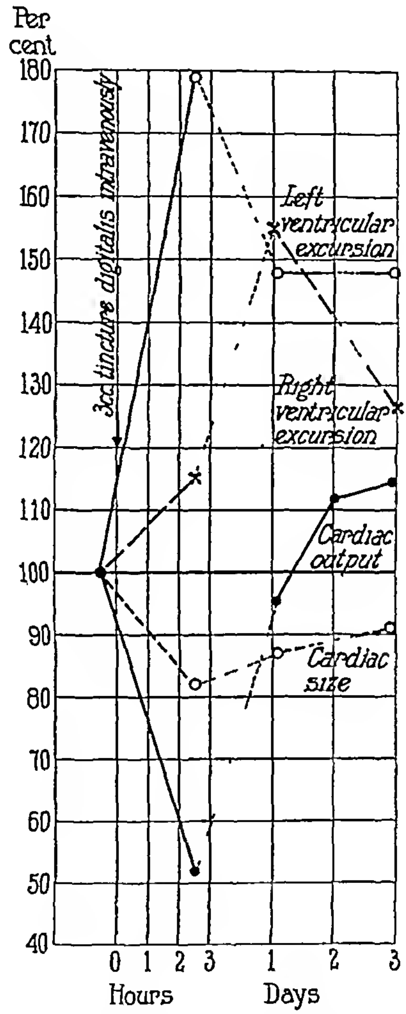

FIG 6 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 258

In this instance, after the preliminary decrease, the cardiac output increased and overshot the initial measurement even though the heart was smaller than it was in the beginning This result is attributed to the fact that the height of the ventricular excursions continued greater than it was in the initial measurements

in heart rate (recorded electrocardiographically) though this was found usually to have decreased 2 to 3 hours after administration Later the rate returned to what it was at the outset of the experiment

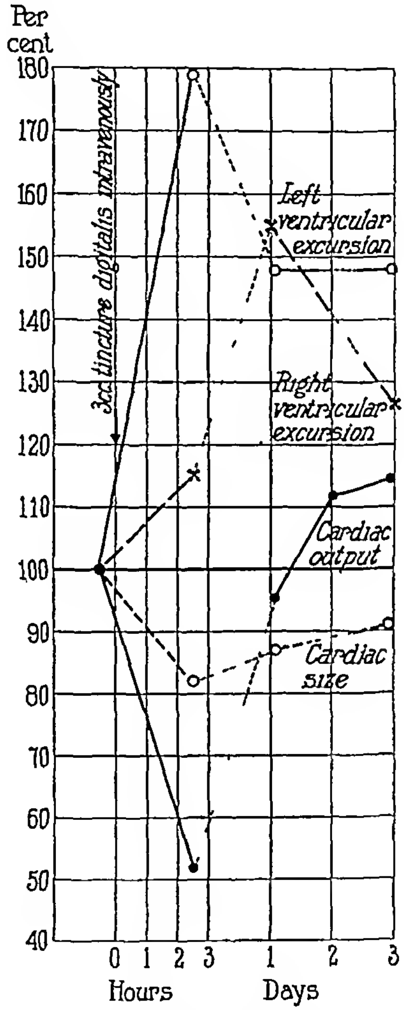

FIG 6 SHOWING THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND EXCURSIONS OF THE RIGHT AND LEFT VENTRICLES IN DOG 258

In this instance, after the preliminary decrease, the cardiac output increased and overshot the initial measurement even though the heart was smaller than it was in the beginning This result is attributed to the fact that the height of the ventricular excursions continued greater than it was in the initial measurements

January 31, 1928 | February 1, 1928 | February 10, 1928

Before digitalis
52 7 sq cm
100 per cent

1 day after
43 8 sq cm
83 per cent

10 days after
51 5 sq cm
98 per cent

Fig 7 Photographs Which Show the Effect of Giving Digitalis on the Size of the Heart of Dog 257

The x-ray photographs were taken on the days indicated Below each photograph is recorded the area of the heart The photographs are reduced to one fourth of their natural size

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TABLE 3

Effect of injecting digitalis upon cardiac output and cardiac size in normal dogs

Dog number and sex	Date	Weight	O_2 content: Arterial	O_2 content: Mixed venous	Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation†: Arterial	O_2 saturation†: Mixed venous	Heart area‡	Heart area per cent of initial	Change in heart area*	Rhythm	Heart rate (electro-cardiogram)	Digitalis given intravenously§	Time after injection of digitalis	Summary of effect on electro cardiogram	Vomited
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	*per cent*	*sq cm*	*per cent*	*per cent*		*per minute*	*cc*	*hours*		
253 Male	November 29, 1927	12 5	15 61	12 61	3 00	122	4 066	100		16 37	94 2	76 5	44 7	100 0		N R.‖	110				
			17 34	11 87	5 47	110	2 193	54	−46	18 66	90 6	63 2	35 7	80 0	−20 0	N R.	90	3 0	2	Decrease in ventricular rate change in T waves	+
	November 30, 1927	11 8	16 31	11 72	4 59	119	2 592	64	−36	17 47	92 2	66 6	37 2	83 0	−17 0	N R.	150		24		
	December 3, 1927	11 5	13 75	9 71	4 04	132	3 267	80	−20	16 73	81 6	57 5	41 8	93 5	−6 5	N R.	150		92		
254 Male	November 28, 1927	14 8	16 02	13 22	2 80	120	4 285	100		16 40	96 4	80 0	43 6	100 0		N R	140				
			17 25	11 96	5 29	124	2 344	55	−45	17 79	95 8	66 8	35 7	82 0	−18 0	Vent. par tach ¶	230	3 3	2	Vent. par tach ¶, change in T-waves	+
	November 29, 1927	13 3	15 50	11 16	4 34	114	2 627	61	−39	16 42	93 2	67 4	38 6	88 5	−11 5	N R	130		25		
	December 2, 1927	13 6	14 18	11 63	2 55	123	4 823	112	+12	14 69	95 2	78 4	43 2	99 0	−1 0	N R.	100		97		
252 Female	December 6, 1927	16 8	20 50	17 58	2 92	181	6 195	100		20 54	98 8	85 2	56 5	100 0		N R.	140				
			20 16	15 81	4 35	175	4 023	65	−35	20 43	97 5	77 0	46 7	83 0	−17 0	N R	90	3 8	2	Ventricular rate decreased, slight change in T waves	+
	December 7, 1927	17 1	19 85	16 26	3 59	186	5 170	83	−17	20 74	94 7	77 9	50 4	89 0	−11 0	N R.	150		26		
	December 10, 1927	17 0	17 05	14 02	3 03	172	5 670	91	−9	18 26	92 3	76 3	50 8	90 0	−10 0	N R.	160		96		

TABLE 3

Effect of injecting digitalis upon cardiac output and cardiac size in normal dogs

Dog number and sex	Date	Weight	O_2 content: Arterial	O_2 content: Mixed venous	Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation†: Arterial	O_2 saturation†: Mixed venous	Heart area‡	Heart area per cent of initial	Change in heart area*	Rhythm	Heart rate (electro-cardiogram)	Digitalis given intravenously§	Time after injection of digitalis	Summary of effect on electro cardiogram	Vomited
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	*per cent*	*sq cm*	*per cent*	*per cent*		*per minute*	*cc*	*hours*		
253 Male	November 29, 1927	12.5	15.61	12.61	3.00	122	4 066	100		16.37	94.2	76.5	44.7	100.0		N R.‖	110				
			17.34	11.87	5.47	110	2 193	54	−46	18.66	90.6	63.2	35.7	80.0	−20.0	N R.	90	3.0	2	Decrease in ventricular rate change in T waves	+
	November 30, 1927	11.8	16.31	11.72	4.59	119	2 592	64	−36	17.47	92.2	66.6	37.2	83.0	−17.0	N R.	150		24		
	December 3, 1927	11.5	13.75	9.71	4.04	132	3 267	80	−20	16.73	81.6	57.5	41.8	93.5	−6.5	N R.	150		92		
254 Male	November 28, 1927	14.8	16.02	13.22	2.80	120	4 285	100		16.40	96.4	80.0	43.6	100.0		N R	140				
			17.25	11.96	5.29	124	2 344	55	−45	17.79	95.8	66.8	35.7	82.0	−18.0	Vent. par tach ¶	230	3.3	2	Vent. par tach ¶, change in T-waves	+
	November 29, 1927	13.3	15.50	11.16	4.34	114	2 627	61	−39	16.42	93.2	67.4	38.6	88.5	−11.5	N R	130		25		
	December 2, 1927	13.6	14.18	11.63	2.55	123	4 823	112	+12	14.69	95.2	78.4	43.2	99.0	−1.0	N R.	100		97		
252 Female	December 6, 1927	16.8	20.50	17.58	2.92	181	6 195	100		20.54	98.8	85.2	56.5	100.0		N R.	140				
			20.16	15.81	4.35	175	4 023	65	−35	20.43	97.5	77.0	46.7	83.0	−17.0	N R	90	3.8	2	Ventricular rate decreased, slight change in T waves	+
	December 7, 1927	17.1	19.85	16.26	3.59	186	5 170	83	−17	20.74	94.7	77.9	50.4	89.0	−11.0	N R.	150		26		
	December 10, 1927	17.0	17.05	14.02	3.03	172	5 670	91	−9	18.26	92.3	76.3	50.8	90.0	−10.0	N R.	160		96		

SUMMARY

Following the administration of digitalis to normal dogs in so-called therapeutic amounts the following effects were observed (1) the form of the T-wave in the electrocardiogram changed, (2) the cardiac output *decreased*, (3) the size of the heart *decreased*, (4) the height of ventricular excursions *increased* When digitalis was excreted all these measurements returned toward normal

DISCUSSION

We have demonstrated then that following the administration of digitalis to normal dogs the cardiac output and the cardiac size *decreased*, but the extent of ventricular contraction on the other hand *increased* In what way are these observations to be connected in analyzing the effect of digitalis on cardiac output? In our early experiments (Cohn and Stewart, 1928a) the six to which reference has just been made and in which cardiac output and cardiac size alone were correlated, there was close agreement between the two, when the cardiac size decreased the cardiac output decreased, as we thought, necessarily But that the influence of digitalis on the two functions was distinct and separable became apparent when the effect of digitalis began to wear off When the size of the heart began to increase, the output sometimes increased more than it should have done were size the only factor involved (dogs 254 and 255, table 3) Why this was so was difficult at first to explain, but the reason became evident as we thought, when we began to take into account the effect of the drug on contraction There was ample reason to anticipate a striking effect on this function based on evidence gained by many other observers from experiments on animals that had been operated on What the effect is in intact animals to which no anesthetic had been given was however unknown The method of the moving film employed in this study permitted an answer to this question, ventricular contraction increases in the intact as it does in the animal which has been operated upon

There are in fact two opposed actions of digitalis, there is an effect on the size of the heart, which we interpret as being an effect on tone, in this case an increase in tone of the heart muscle, from

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output, we have attempted to study by plotting systematically all the measurements of size that we have made in all the dogs and of correlating them with the corresponding simultaneous volume outputs (fig 8) The sizes (not grouped from the point of view of their origin in individual dogs) are arranged in decreasing order (table 1, column 14 and table 3, column 15) It will be observed that as the

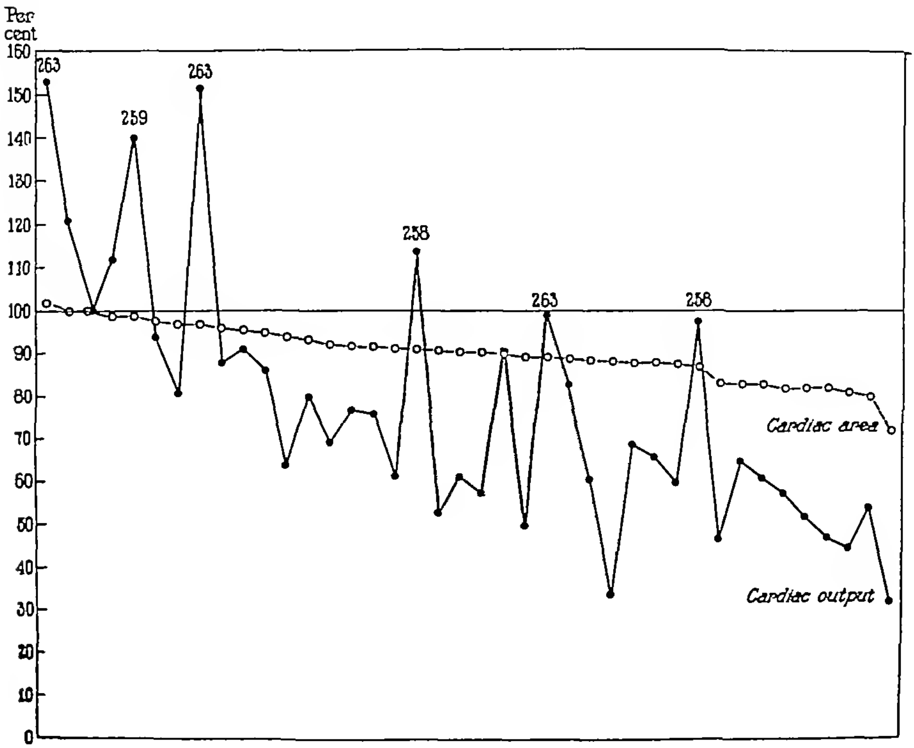

FIG 8 SHOWING THE CORRELATION BETWEEN CARDIAC SIZE AND CARDIAC OUTPUT

For explanation see the text

areas of the hearts decrease, volume outputs also decrease consistently, though these naturally fluctuate The slope of the curve of cardiac output is greater than that of heart area The difference is to be expected since cardiac output is a cubic, while the heart area is a square measurement Were it not that we have data on differences in the extent of the ventricular excursions we should be unable

output, we have attempted to study by plotting systematically all the measurements of size that we have made in all the dogs and of correlating them with the corresponding simultaneous volume outputs (fig 8) The sizes (not grouped from the point of view of their origin in individual dogs) are arranged in decreasing order (table 1, column 14 and table 3, column 15) It will be observed that as the

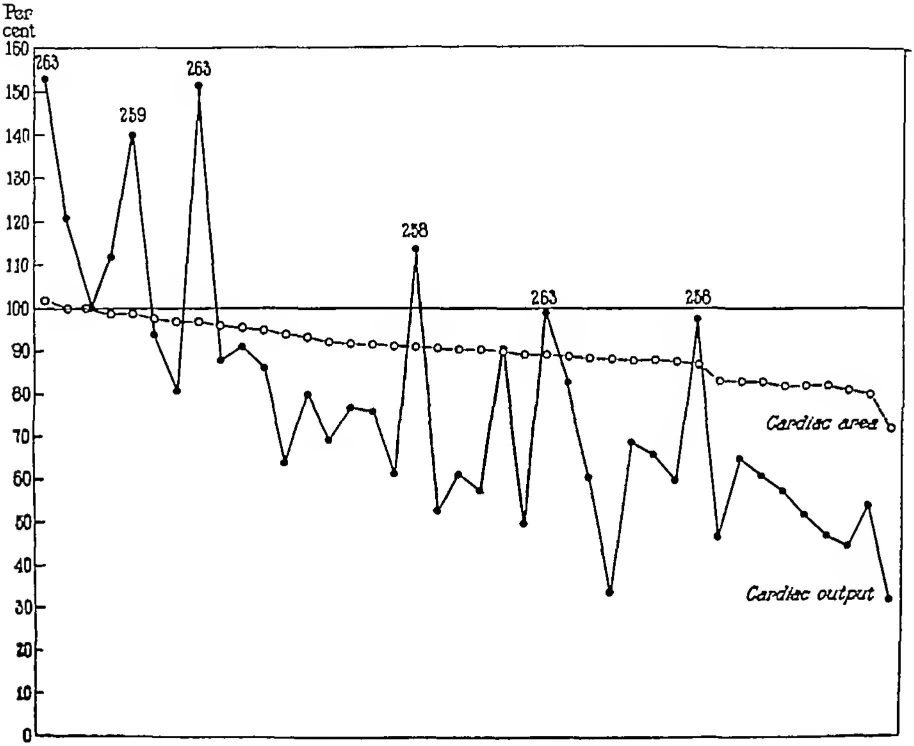

FIG 8 SHOWING THE CORRELATION BETWEEN CARDIAC SIZE AND CARDIAC OUTPUT

For explanation see the text

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SUMMARY

The effect of therapeutic doses of digitalis given intravenously and by mouth upon the circulation of normal dogs has been studied It was found that

1 Changes in T-waves of the electrocardiograms were constantly observed

2 The heart rate always slowed 2 to 3 hours after giving digitalis unless an abnormal rhythm developed In 24 hours the rate was like the initial count

3 The cardiac area decreased

4 The ventricular excursions increased

5 The cardiac output always decreased at first, but might later increase

6 These effects were at a maximum 2 to 24 hours after the administration of the drug

7 As the effect of digitalis wore off the cardiac output, cardiac size and ventricular excursions returned to normal The cardiac output often became greater than the initial value

CONCLUSIONS

Digitalis within the first 24 hours decreases the cardiac output of normal dogs The cardiac output which obtains at any later instant is the net result of the working of two opposing factors The first of these effects increases cardiac tone and results in decrease in the size of the heart It is due to this action that cardiac output tends to decrease The second effect increases ventricular contraction and tends to increase cardiac output If cardiac size is not smaller than a critical value, increase in ventricular contraction overbalances decrease in size so that cardiac output increases beyond the beginning value

BIBLIOGRAPHY

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SUMMARY

The effect of therapeutic doses of digitalis given intravenously and by mouth upon the circulation of normal dogs has been studied. It was found that

1. Changes in T-waves of the electrocardiograms were constantly observed.
2. The heart rate always slowed 2 to 3 hours after giving digitalis unless an abnormal rhythm developed. In 24 hours the rate was like the initial count.
3. The cardiac area decreased.
4. The ventricular excursions increased.
5. The cardiac output always decreased at first, but might later increase.
6. These effects were at a maximum 2 to 24 hours after the administration of the drug.
7. As the effect of digitalis wore off the cardiac output, cardiac size and ventricular excursions returned to normal. The cardiac output often became greater than the initial value.

CONCLUSIONS

Digitalis within the first 24 hours decreases the cardiac output of normal dogs. The cardiac output which obtains at any later instant is the net result of the working of two opposing factors. The first of these effects increases cardiac tone and results in decrease in the size of the heart. It is due to this action that cardiac output tends to decrease. The second effect increases ventricular contraction and tends to increase cardiac output. If cardiac size is not smaller than a critical value, increase in ventricular contraction overbalances decrease in size so that cardiac output increases beyond the beginning value.

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MATERIAL

The dogs which were studied were operated on $2\frac{1}{6}$ to $4\frac{1}{12}$ years ago Evidence of the lesions which were then created were still present at the time of these experiments (table 1) Complete data concerning the operations in these animals will be published later (Stewart) A brief description only of the method used in operating on the valves need be given Under ether and under aseptic conditions the left auricular appendage was exposed and incised A cardioscope[1] was then inserted through this opening and placed so that the leaflets of

TABLE 1

Enlargement of the heart following induction of artificial mitral insufficiency in dogs

Dog number	Area of heart* before operation	Area of heart* after operation	Time since operation	Increase in heart area
	sq cm	*sq cm*	*years*	*per cent*
155	56 1	66 1	$2\frac{1}{3}$	18
158	46 4	84 3	$2\frac{1}{3}$	82
		90 2	$3\frac{1}{3}$	94
161	46 0	71 4	$2\frac{1}{2}$	55
		81 2	$3\frac{1}{4}$	77
162	55 0	65 8	$2\frac{1}{2}$	20
		66 9	$3\frac{1}{6}$	22
171	50 3	62 3	$2\frac{1}{6}$	24
90	43 0	45 3	$4\frac{1}{12}$	5

* The x ray photographs were made at a distance of 2 meters

the mitral valve were brought into view The leaflet could then be cut under direct vision Development of a marked systolic thrill was

[1] The cardioscope which we used was designed with the assistance of Mr R Wappler, and was made for us by the Wappler Electric Company, Long Island City, New York The idea of cutting the valves of the heart under direct vision was suggested to us by the preliminary report, of Allen and Graham (1922) As complete data for the construction of their instrument was not available at the time, we devised this new instrument. The optical system is similar to that used in cystoscopes We are much indebted to Doctors Graham and Allen for valuable aid in learning their methods and desire to express our thanks to them for their courtesy

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161	46 0	71 4	$2\frac{1}{2}$	55
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Effect of digitalis on cardiac output, cardiac size and ventricula

Dog number and sex	Date	Weight	O₂ content: Arterial	O₂ content: Mixed venous	Arterio venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 satura[tion]: Arterial	
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	
162 Female	May 23, 1927	17 1	18 84	16 73	2 11	106	5,024	100 0		19 80	94 1	8
			21 97	17 00	4 97	106	2,133	42 0	−58 0	22 00	98 9	7
	May 24, 1927		19 04	16 42	2 62	111	4,237	84 0	−16 0	20 03	94 1	8
	May 25, 1927		18 86	15 10	3 76	122	3,249	64 0	−36 0	19 78	94 3	7
	May 27, 1927		16 53	13 86	2 67	119	4,459	89 0	−11 0	16 80	97 2	8
	June 1, 1927		13 75	11 96	1 74	124	7,084	120 0	+20 0	14 91	98 5	8
	March 19, 1928	17 4	15 51	13 77	1 74	116	6,663	100 0		16 04	95 5	8
			18 43	13 46	4 97	109	2,163	32 9	−67 1	20 02	91 1	6
	March 20, 1928	16 5	17 31	13 55	3 76	109	2,900	43 5	−56 5	18 50	92 5	[illegible]
	March 21, 1928	15 9	15 70	11 79	3 91	106	2,710	41 3	−58 7	16 45	94 2	7
	March 29, 1928	14 5	14 05	10 08	3 97	98	2,468	100 0		14 98	92 4	6
			15 42	9 69	5 73	95	1,657	67 2	−32 8	16 48	92 3	[illegible]
	March 30, 1928	13 5	14 27	10 08	4 19	96	2,292	92 9	−7 1	15 65	90 0	6
	April 2, 1928	13 6	12 76	8 86	3 90	98	2,538	102 7	+2 7	13 99	89 8	6
161 Male	June 6, 1927	14 8	17 11	15 34	1 77	154	8,700	100 0		17 94	94 2	8
			18 86	14 58	4 28	144	3,365	38 0	−62 0	19 82	94 1	[illegible]
	June 7, 1927		18 82	15 08	3 74	148	3,959	45 0	−55 0	19 20	96 9	[illegible]
	June 8, 1927		17 36	12 99	4 37	138	3,159	36 0	−64 0	18 10	94 8	[illegible]
	June 10, 1927		14 76	12 99	1 77	133	7,514	86 0	−14 0	15 28	96 7	8

* In this column, + indicates increase, and − decrease

† Before calculating the oxygen saturations 0 2 and 0 1 volume per cent (the amount of oxygen in phy[sical] solution) were subtracted from the arterial and mixed venous oxygen contents respectively

§ Tincture of digitalis unless otherwise indicated

‖ N R = normal rhythm, A.F = auricular fibrillation, V P C = ventricular premature contract[ions], A P C = auricular premature contractions, Vent. Par Tach = ventricular paroxysmal tachycardia, I- incomplete heart block, +P-R = conduction time increased

TABLE 2

Effect of digitalis on cardiac output, cardiac size and ventricular contraction (excursion) in do

Dog number and sex	Date	Weight	O₂ content: Arterial	O₂ content: Mixed venous	Arterio venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation†: Arterial	O_2 saturation†: Mixed venous	Analysis of stationary films: Heart area	Heart area per cent of initial	Change in heart area*	Rib or intercostal space photographed	Left ventricular exc[ursion]
		kgm	volumes per cent	volumes per cent	volumes per cent	cc per minute	cc	per cent	per cent	volumes per cent	per cent	per cent	sq cm.	per cent	per cent		
162 Female	May 23, 1927	17 1	18 84	16 73	2 11	106	5,024	100 0		19 80	94 1	85	65 8‡	100 0			
			21 97	17 00	4 97	106	2,133	42 0	−58 0	22 00	98 9	78	49 0‡	74 4	−25 6		
	May 24, 1927		19 04	16 42	2 62	111	4,237	84 0	−16 0	20 03	94 1	81	61 6‡	93 6	−6 4		
	May 25, 1927		18 86	15 10	3 76	122	3,249	64 0	−36 0	19 78	94 3	7[illegible]	55 5‡	84 3	−15 [illegible]		
	May 27, 1927		16 53	13 86	2 67	119	4,459	89 0	−11 0	16 80	97 2	82	62 4‡	94 9	−5 1		
	June 1, 1927		13 75	11 96	1 74	124	7,084	120 0	+20 0	14 91	98 5	86	65 4‡	100 0			
	March 19, 1928	17 4	15 51	13 77	1 74	116	6,663	100 0		16 04	95 5	8[illegible]	78 5	100 0			
			18 43	13 46	4 97	109	2,163	32 9	−67 1	20 02	91 1	66	67 [illegible]	79 8	−20 2		
	March 20, 1928	16 5	17 31	13 55	3 76	109	2,900	43 5	−56 5	18 50	92 5	[illegible]	70 [illegible]	90 1	−9 9		
	March 21, 1928	15 9	15 70	11 79	3 91	106	2,710	41 3	−58 7	16 45	94 2	71	71 2	90 7	−9 3		
	March 29, 1928	14 5	14 05	10 08	3 97	98	2,468	100 0		14 98	92 4	6[illegible]	70 2	100 0		6th rib	2 1
			15 42	9 69	5 73	95	1,657	67 2	−32 8	16 48	92 3	5[illegible]	57 3	81 6	−18 4	6th rib	3 [illegible]
	March 30, 1928	13 5	14 27	10 08	4 19	96	2,292	92 9	−7 1	15 65	90 0	6[illegible]	60 6	86 4	−13 6	6th rib	[illegible] 8
	April 2, 1928	13 6	12 76	8 86	3 90	98	2,538	102 7	+2 7	13 99	89 8	6[illegible]	63 8	90 9	−9 1	6th rib	3 4
161 Male	June 6, 1927	14 8	17 11	15 34	1 77	154	8,700	100 0		17 94	94 2	8[illegible]	71 4‡	100 0			
			18 86	14 58	4 28	144	3,365	38 0	−62 0	19 82	94 1	[illegible]	57 6‡	80 [illegible]	−19 3		
	June 7, 1927		18 82	15 08	3 74	148	3,959	45 0	−55 0	19 20	96 9	[illegible]	61 5‡	86 1	−13 9		
	June 8, 1927		17 36	12 99	4 37	138	3,159	36 0	−64 0	18 10	94 8	[illegible]	59 9‡	83 8	−16 2		
	June 10, 1927		14 76	12 99	1 77	133	7,514	86 0	−14 0	15 28	96 7	8[illegible]	67 2‡	94 1	−5 9		

* In this column, + indicates increase, and − decrease

† Before calculating the oxygen saturations 0 2 and 0 1 volume per cent (the amount of oxygen in ph[ysical] solution) were subtracted from the arterial and mixed venous oxygen contents respectively

‡ The x ray photographs from wh[ich] ... all others at a distance of 34 inches

§ Tincture of digitalis unless otherwise indicated

¶ 1.0 cc. of this was given

|| N R = normal rhythm, A.F = auricular fibrillation, V P C = ventricular premature contract[ions], A P C = auricular premature contractions, Vent. Par Tach = ventricular paroxysmal tachycardia, I-H B = incomplete heart block, +P-R = conduction time increased

** 2.6 cc. of this was given su[bcutaneously]

TABLE 2

Dog number and sex	Date	Weight	O₂ content		Arterio venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation	
			Arterial	Mixed venous							Arterial	Mixed venous
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	*per cen.*
161 Male (continued)	March 27, 1928	13 9	17 67	15 10	2 57	104	4,048	100 0		18 95	92 2	79
			19 91	15 96	3 95	109	2,760	68 2	−31 8	21 70	90 9	73
	March 28, 1928	13 0	20 59	14 15	6 44	105	1,630	40 3	−59 7	22 40	91 0	62
	March 31, 1928	13 0	17 64	12 97	4 67	108	2,313	57 2	−42 8	18 55	94 0	69
158 Male	May 31, 1927	20 2	20 32	19 04	1 28	128	10,000	100 0		21 17	95 0	89
			19 08	14 00	5 08	126	2,480	25 0	−75 0	19 85	95 8	70
	June 1, 1927		20 34	16 80	3 52	136	3,841	38 0	−62 0	21 59	94 2	77
	June 2, 1927		18 77	16 73	2 04	142	6,960	70 0	−30 0	19 67	94 4	84
	June 9, 1927	19 2	16 91	15 39	1 52	130	8,553	100 0		17 45	95 7	87
			20 41	15 37	5 04	131	2,600	35 0	−65 0	21 64	93 3	70
	June 10, 1927		19 44	14 58	4 86	111	2,284	27 0	−73 0	21 21	90 7	68
	June 11, 1927		16 66	13 73	2 93	112	3,823	45 0	−55 0	18 08	91 0	75
	March 22, 1928	20 3	20 60	18 66	1 94	126	6,500	100 0		21 38	95 5	86
			22 78	19 30	3 48	119	3,418	52 6	−47 4	24 47	92 3	78
	March 23, 1928	18 3	23 20	17 90	5 30	126	2,370	36 5	−63 5	24 07	95 6	74
	March 24, 1928	17 9	21 27	18 34	2 93	132	4,510	69 4	−30 6	22 88	92 1	79
	March 26, 1928	18 5	19 02	14 86	4 16	123	2,960	45 6	−55 4	20 37	92 4	72

TABLE

Dog number and sex	Date	Weight	O_2 content: Arterial	O_2 content: Mixed venous	Arterio venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturat…: Arterial	…
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	
161 Male (continued)	March 27, 1928	13 9	17 67	15 10	2 57	104	4,048	100 0		18 95	92 2	7
			19 91	15 96	3 95	109	2,760	68 2	−31 8	21 70	90 9	7
	March 28, 1928	13 0	20 59	14 15	6 44	105	1,630	40 3	−59 7	22 40	91 0	6
	March 31, 1928	13 0	17 64	12 97	4 67	108	2,313	57 2	−42 8	18 55	94 0	6
158 Male	May 31, 1927	20 2	20 32	19 04	1 28	128	10,000	100 0		21 17	95 0	8
			19 08	14 00	5 08	126	2,480	25 0	−75 0	19 85	95 8	7
	June 1, 1927		20 34	16 80	3 52	136	3,841	38 0	−62 0	21 59	94 2	7
	June 2, 1927		18 77	16 73	2 04	142	6,960	70 0	−30 0	19 67	94 4	84
	June 9, 1927	19 2	16 91	15 39	1 52	130	8,553	100 0		17 45	95 7	87
			20 41	15 37	5 04	131	2,600	35 0	−65 0	21 64	93 3	70
	June 10, 1927		19 44	14 58	4 86	111	2,284	27 0	−73 0	21 21	90 7	68
	June 11, 1927		16 66	13 73	2 93	112	3,823	45 0	−55 0	18 08	91 0	75
	March 22, 1928	20 3	20 60	18 66	1 94	126	6,500	100 0		21 38	95 5	86
			22 78	19 30	3 48	119	3,418	52 6	−47 4	24 47	92 3	78
	March 23, 1928	18 3	23 20	17 90	5 30	126	2,370	36 5	−63 5	24 07	95 6	74
	March 24, 1928	17 9	21 27	18 34	2 93	132	4,510	69 4	−30 6	22 88	92 1	79
	March 26, 1928	18 5	19 02	14 86	4 16	123	2,960	45 6	−55 4	20 37	92 4	72

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Dog number and sex	Date	Weight	O₂ content		Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation	
			Arterial	Mixed venous							Arterial	Mixed venous
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	*per cent*
155 Female	May 16, 1927	31 9	20 18	17 60	2 58	161	6,240	100 0		21 95	91 0	80
			20 78	16 75	4 05	143	3,531	56 0	−44 0	21 24	92 5	74
	May 17, 1927		20 58	17 56	3 02	173	5,728	92 0	−8 0	21 28	95 8	82 1
	May 18, 1927		19 69	17 16	2 53	154	6,088	98 0	−2 0	20 36	95 7	83 9
	May 19, 1927		18 77	16 13	2 64	155	5,871	94 0	−6 0	19 24	96 5	83 3
171 Female	June 7, 1927	16 4	20 85	19 10	1 75	158	9,028	100 0		21 73	95 0	87 5
			23 43	12 92	10 51	162	1,541	17 0	−83 0	24 35	95 4	52 7
	June 8, 1927		25 00	11 76	13 24	173	1,307	14 0	−86 0	26 30	94 3	43
	June 9, 1927											
90 Male	March 26, 1928	10 6	19 48	16 22	3 26	59	1,810	100 0		20 31	95 0	79 4
			22 22	17 99	4 23	59	1,395	77 0	−23 0	23 17	95 1	77 2
	March 27, 1928	9 9	20 66	8 57	12 09	59	488	27 0	−73 0	23 02	92 9	38 5

TABLE 2

Dog number and sex	Date	Weight	O_2 content		Arterio-venous oxygen difference	Oxygen consumption	Cardiac output per minute	Cardiac output per cent of initial	Change in cardiac output*	O_2 capacity	O_2 saturation†	
			Arterial	Mixed venous							Arterial	Mixed venous
		kgm	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc per minute*	*cc*	*per cent*	*per cent*	*volumes per cent*	*per cent*	*per cent*
155 Female	May 16, 1927	31 9	20 18	17 60	2 58	161	6,240	100 0		21 95	91 0	80 0
			20 78	16 75	4 05	143	3,531	56 0	−44 0	21 24	92 5	74 8
	May 17, 1927		20 58	17 56	3 02	173	5,728	92 0	−8 0	21 28	95 8	82 1
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			23 43	12 92	10 51	162	1,541	17 0	−83 0	24 35	95 4	52 7
	June 8, 1927		25 00	11 76	13 24	173	1,307	14 0	−86 0	26 30	94 3	43 6
	June 9, 1927											
90 Male	March 26, 1928	10 6	19 48	16 22	3 26	59	1,810	100 0		20 31	95 0	79 4
			22 22	17 99	4 23	59	1,395	77 0	−23 0	23 17	95 1	77 2
	March 27, 1928	9 9	20 66	8 57	12 09	59	488	27 0	−73 0	23 02	92 9	38 5

OBSERVATIONS

Effect of digitalis on cardiac output Mitral insufficiency was created in dog 162 on January 13, 1925, $2\frac{1}{2}$ years ago The heart area increased 20 per cent during this time, from 55 0 to 65 8 sq cm (table 1) The cardiac output on May 23, 1927, was 5024 cc per minute (table 2) Two hours after injection of tincture of digitalis 3 5 cc, the output decreased to 2133 cc per minute, 23 hours after, it increased to 4237 cc, 45 hours after it fell to 3249 cc, $81\frac{1}{2}$ hours after it was 4459 cc, and $103\frac{1}{2}$ hours after, 7084 cc The decrease (58 per cent) in cardiac output was at a maximum 2 hours after digitalis was given The output returned to normal with slight fluctuations toward the end of the 8th day

On March 19, 1928, the experiment was repeated $3\frac{1}{6}$ years after the first operation The heart had enlarged 22 per cent (table 1) The cardiac output was 6663 cc per minute (table 2) Tincture of digitalis 4 0 cc was then administered intravenously Three hours later the output fell to 2193 cc but increased the following day to 2900 cc The output had not returned to normal 9 days later and was only 2468 cc per minute On March 29, tincture of digitalis 2 3 cc was again injected intravenously, and was followed by a fall in cardiac output to 1657 cc or 67 2 per cent of the initial measurement, in 3 hours (table 2, fig 1) At the end of four days the cardiac output returned to 2535 cc or 102 7 per cent of the output at the beginning of this period (March 29, 1928) On three occasions accordingly the administration of digitalis in this dog was followed by decreases in cardiac output

Mitral insufficiency was created in dog 161 in December 11, 1924, $2\frac{1}{2}$ years ago During this time the area of the heart increased 55 per cent from 46 0 to 71 4 sq cm (table 1) The cardiac output was estimated on June 6, 1927, and found to be 8700 cc per minute (table 2) Tincture of digitalis 3 3 cc was then given intravenously When estimated 2 hours later the output was found to have decreased to 3365 cc per minute The measurement 21 hours after injection rose to 3959 cc, but after 48 hours it again fell to 3159 cc, after 96 hours it increased to 7514 cc There was accordingly a decrease of 62 per cent in cardiac output immediately after giving digitalis At the end of four days the effect had nearly worn off

OBSERVATIONS

Effect of digitalis on cardiac output Mitral insufficiency was created in dog 162 on January 13, 1925, $2\frac{1}{2}$ years ago The heart area increased 20 per cent during this time, from 55 0 to 65 8 sq cm (table 1) The cardiac output on May 23, 1927, was 5024 cc per minute (table 2) Two hours after injection of tincture of digitalis 3 5 cc, the output decreased to 2133 cc per minute, 23 hours after, it increased to 4237 cc, 45 hours after it fell to 3249 cc, $81\frac{1}{2}$ hours after it was 4459 cc, and $103\frac{1}{2}$ hours after, 7084 cc The decrease (58 per cent) in cardiac output was at a maximum 2 hours after digitalis was given The output returned to normal with slight fluctuations toward the end of the 8th day

On March 19, 1928, the experiment was repeated $3\frac{1}{6}$ years after the first operation The heart had enlarged 22 per cent (table 1) The cardiac output was 6663 cc per minute (table 2) Tincture of digitalis 4 0 cc was then administered intravenously Three hours later the output fell to 2193 cc but increased the following day to 2900 cc The output had not returned to normal 9 days later and was only 2468 cc per minute On March 29, tincture of digitalis 2 3 cc was again injected intravenously, and was followed by a fall in cardiac output to 1657 cc or 67 2 per cent of the initial measurement, in 3 hours (table 2, fig 1) At the end of four days the cardiac output returned to 2535 cc or 102 7 per cent of the output at the beginning of this period (March 29, 1928) On three occasions accordingly the administration of digitalis in this dog was followed by decreases in cardiac output

Mitral insufficiency was created in dog 161 in December 11, 1924, $2\frac{1}{2}$ years ago During this time the area of the heart increased 55 per cent from 46 0 to 71 4 sq cm (table 1) The cardiac output was estimated on June 6, 1927, and found to be 8700 cc per minute (table 2) Tincture of digitalis 3 3 cc was then given intravenously When estimated 2 hours later the output was found to have decreased to 3365 cc per minute The measurement 21 hours after injection rose to 3959 cc, but after 48 hours it again fell to 3159 cc, after 96 hours it increased to 7514 cc There was accordingly a decrease of 62 per cent in cardiac output immediately after giving digitalis At the end of four days the effect had nearly worn off

The experiment was repeated 9 months later on March 27, 1928 It was now $3\frac{1}{4}$ years since operation The heart had increased in size 77 per cent (table 1) The cardiac output was 4048 cc per minute (table 2) Tincture of digitalis 2 6 cc was given intravenously and 0 5 cc subcutaneously The output fell 3 hours later to 2760 cc and 24 hours later still further, to 1630 cc It rose to 2313 cc 4 days after injection There was then a maximum fall of 60 per cent in cardiac output followed by return toward normal

Mitral insufficiency was created in dog 158 on December 2, 1924, $2\frac{1}{2}$ years ago The area of the heart increased (82 per cent) from 46 4 to 84 3 sq cm (table 1) The cardiac output on May 31, 1927 was 10,000 cc per minute (table 2) Two hours after the injection of tincture of digitalis 4 6 cc the output fell to 2480 cc , 20 hours after, it rose to 3841 cc , and 45 hours after, it rose further to 6960 cc A week later it rose still further to 8553 cc , nearly to the level existing before digitalis was administered On June 6, 1927, tincture of digitalis 4 4 cc was given again Two hours later the output decreased to 2600 cc per minute, and 24 hours afterward decreased further to 2284 cc At the end of 47 hours the cardiac output began to increase and was found to be 3823 cc The output decreased then 75 per cent following the administration of digitalis and slowly returned toward normal

Digitalis was given again 10 months later Mitral insufficiency had now been established for $3\frac{1}{3}$ years During this time the heart area increased 94 per cent from 46 4 sq cm to 90 2 sq cm (table 1) The cardiac output on March 22, 1928 was 6500 cc per minute (table 2) Tincture of digitalis 4 3 cc was injected intravenously The output fell 3 hours later to 3418 cc , 1 day later it fell further to 2370 cc , 1 day later still it increased to 4510 cc and 2 days later, that is to say, 4 days after injection it fell again to 2960 cc There was a maximum decrease (64 per cent) in cardiac output 25 hours after the injection of digitalis, followed by a slow return toward normal On three occasions the same result followed the administration of digitalis, there was always a decrease in cardiac output

Mitral insufficiency was created in dog 155 on February 25, 1925, $2\frac{1}{2}$ years ago After this the dog became pregnant and was delivered of 5 puppies without developing any signs of heart failure The area

The experiment was repeated 9 months later on March 27, 1928 It was now 3¼ years since operation The heart had increased in size 77 per cent (table 1) The cardiac output was 4048 cc per minute (table 2) Tincture of digitalis 2 6 cc was given intravenously and 0 5 cc subcutaneously The output fell 3 hours later to 2760 cc and 24 hours later still further, to 1630 cc It rose to 2313 cc 4 days after injection There was then a maximum fall of 60 per cent in cardiac output followed by return toward normal

Mitral insufficiency was created in dog 158 on December 2, 1924, 2½ years ago The area of the heart increased (82 per cent) from 46 4 to 84 3 sq cm (table 1) The cardiac output on May 31, 1927 was 10,000 cc per minute (table 2) Two hours after the injection of tincture of digitalis 4 6 cc the output fell to 2480 cc , 20 hours after, it rose to 3841 cc , and 45 hours after, it rose further to 6960 cc A week later it rose still further to 8553 cc , nearly to the level existing before digitalis was administered On June 6, 1927, tincture of digitalis 4 4 cc was given again Two hours later the output decreased to 2600 cc per minute, and 24 hours afterward decreased further to 2284 cc At the end of 47 hours the cardiac output began to increase and was found to be 3823 cc The output decreased then 75 per cent following the administration of digitalis and slowly returned toward normal

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Mitral insufficiency was created in dog 155 on February 25, 1925, 2½ years ago After this the dog became pregnant and was delivered of 5 puppies without developing any signs of heart failure The area

as an example On March 19, 1928, the area of the heart was 78 5 sq cm (table 2) Digitalis was then administered and three hours later the area diminished to 62 7 sq cm, 79 8 per cent of the initial value There was an increase 2 days later to 71 2 sq cm or 90 7 per cent of the first measurement Ten days later, on March 29, 1928, digitalis was again injected The area of the heart at this time was 70 2 sq cm (table 2, figs 1 and 3) Three hours afterward the area decreased to 57 3 sq cm or 81 6 per cent of the size before this injection The area increased slightly to 60 6 sq cm 24 hours later, or 86 4 per cent The size 4 days later increased still more to 63 8 sq cm or 90 9 per cent On both occasions the size of the heart decreased within 24 hours, 20 and 18 per cent respectively Then it gradually increased as the effect of digitalis wore off This dog had been given digitalis 9 months before (table 2) and on this occasion also there was a decrease in size of 25 6 per cent

The effect of digitalis in the other dogs was similar to that just described Digitalis was given to dog 161 on two occasions (table 2), to dog 171 once (table 2), to dog 155 once (table 2), to dog 158 on three occasions (table 2) and to dog 90 once (table 2, fig 2) The greatest decrease detected occurred sometimes at 2½ hours and at other times 24 hours after the injection of digitalis and varied in extent between 11 and 29 per cent Decrease was followed by increase in size as the effect of digitalis diminished

Effect of digitalis on ventricular contraction of enlarged hearts On March 29, 1928 in dog 162 the *left* ventricular excursion was 2 1 mm at the level of the 6th rib (table 2, figs 1 and 4) Digitalis was then given The *left* ventricular excursion 3 hours later was 3 7 mm At the end of the first day it was 3 8 mm, and at the end of the fourth, it was 3 4 mm The *right* ventricular excursion increased from 3 6 mm to a maximum of 7 3 mm The maximum increase of the left ventricular excursion was accordingly 1'81 per cent and of the right 200 per cent As the effect of digitalis wore off the excursions became small

There are observations like these in 3 other dogs (table 2, fig 2) All behaved alike The increase in height of excursion of the left ventricle ranged between 16 and 81 per cent Whenever right ventricular excursions could be measured, increases attaining 100 per cent were observed In all cases, measurement was however not possible

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Effect of digitalis on rate conduction time and on the form of the electrocardiogram Changes in the form of the T-wave were constantly found following the administration of digitalis (tables 2 and 3) The ventricular rate was sometimes increased, sometimes decreased and at other times unchanged The conduction time was increased in 3

TABLE 3

Summary of effect of digitalis on the electrocardiograms of dogs with enlarged hearts

Dog number	Date	Ventricular rate	P R interval	T waves	Abnormalities due to digitalis	Degree of enlargement of heart
						per cent
90	March 26, 1928	0	0	c	Vent Par Tach.	5
158	May 31, 1927	–	+	c	A P C	82
	June 9, 1927	+	+	c	Vent. Par Tach	82
	March 22, 1928	+	+	c	Aur Fib , V P C	94
155	May 16, 1927	–	+	c	None	18
161	June 6, 1927	–	0	c	None	55
	March 27, 1928	+	0	c	Runs of Vent Par Tach.	77
162	May 23, 1927	0	0	c	V P C	20
	March 19, 1928	0	+	c	I-H B	22
	March 29, 1928	0	0	c	None	22
171	June 7, 1927	+	0	c	None	24

c = changed, 0 = unchanged, + = increased, – = decreased Vent Par Tach = Ventricular paroxysmal tachycardia A P C = Auricular premature contractions Aur fib = Auricular fibrillation V P C = Ventricular premature contractions I-H B = Incomplete heart block

Fig 4 In this figure are reproduced photographs of the moving films obtained in the manner described in the preceding paper (Cohn and Stewart, 1928) Below each photograph are placed tracings of the original films which show the excursions made by the right and left ventricles respectively When these photographs were taken the time marker was not working properly The film was moving however, at a constant speed The photographs are reduced to one-fourth of their natural size

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dogs (dogs 155, 158 and 162) Evidence of toxic action was manifested in the form of irregularity in all dogs except 155 and 171 Paroxysmal ventricular tachycardia was encountered in 3 dogs (dogs 90, 158 and 161) Auricular premature contractions were observed once (dog 158), ventricular premature contractions (without paroxysmal ventricular tachycardia) twice (dogs 158 and 162), incomplete heart block once (dog 162) and auricular fibrillation once (dog 158) These effects were all transient and occurred at the height of the action of digitalis

DISCUSSION

In the light of these experiments it appears that the effect of giving digitalis results just as was the case in normal dogs in decreasing the cardiac output and the size of the heart and in increasing the height of ventricular excursions in dogs in which the hearts are enlarged but in which the signs of heart failure have not developed Whether enlargement was due to dilatation or to hypertrophy or to both we do not know, for most of the animals are still alive There can be no doubt however that at the time of observation they were in a state of compensation, for they ran on a treadmill as long and with as great ease as did normal dogs

As in normal dogs, giving digitalis increased the tone of heart muscle, an effect which is reflected in the decreased size of the heart The cardiac output was in consequence also decreased Again as in normal dogs contraction increased, the result of which tended to increase cardiac output And finally, the effect on cardiac output which depends upon the net result of the interaction of these two functions varied For the first 24 hours the effect on tone overbalanced that on contraction so that cardiac output was uniformly decreased But when the action of digitalis began to diminish, the rate at which it did so, differed in the various functions, so that the effect on contraction measured in terms of the height of the ventricular excursions exceeded the effect on tone, estimated in terms of the size of the heart, or persisted long after the effect upon it (tone) began to diminish In such instances, the cardiac output returned to normal or overshot this mark, due to the increased extent of ventricular excursion, even though the heart sometimes continued to be smaller than it had been in the beginning (dog 162, (table 2 and fig 1)

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two curves We believe we are correct in referring the irregularities to the influence of ventricular contraction Where the peaks occur, increase in the height of excursion was great enough to effect cardiac output, increase in excursion then overbalanced decrease in size and permitted an excess in output beyond that which would have been anticipated from the slope of the curve All of this, as well as the origin of the blood responsible for the unlooked for results are discussed also in the preceding paper

Two dogs (dogs 90 and 171, table 2) died following the administration of digitalis The cardiac size was decreased in them as much as 25 per cent below the original measurement and the cardiac output 73 and 86 per cent respectively Whether death was due to the inability of the small heart to pump enough blood to maintain life, or whether it was due to a toxic effect on the heart muscle we do not know Paroxysmal ventricular tachycardia occurred in dog 90, but the normal rhythm continued to be present in dog 171 (table 2)

The changes in the electrocardiograms were on the whole more pronounced in these dogs than in the normal ones An effect was found constantly in form of the T-waves (tables 2 and 3) Auriculo-ventricular conduction time increased in 3 dogs (dogs 155, 158 and 162) and on each of the 3 occasions on which digitalis was given to dog 158 (table 3) Abnormal rhythms (paroxysmal ventricular tachycardia, auricular fibrillation and incomplete heart block) as well as ectopic beats of auricular and ventricular origin were encountered They were found perhaps more frequently in this group than in the normal dogs That abnormal mechanisms are expected when digitalis is prescribed in large hearts oftener and rather than in normal ones is a consequence of clinical experience But whether their occurrence is a result of size merely or whether both size and irregularity of action are dependent on a common underlying fault is not yet, so far as we know, understood

The fact has been mentioned that dog 90 did not show cardiac enlargement (table 1) At the time of operation a soft systolic murmur appeared at the mitral area and persisted for several months Then it disappeared leaving only a sharp first sound Since cardiac enlargement did not develop in the absence of the murmur it is probable that no lesion of sufficient extent resulted from the operation

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Regen (1927) showed Though the heart does not become smaller, an influence on its size may nevertheless be demonstrated, as was shown by Levy (1923) in the case of lobar pneumonia In this disease enlargement of the heart did not take place, or at least tended to occur less frequently if this drug was given We have ourselves shown that in patients increase in ventricular excursions may take place after digitalis administration (Cohn and Stewart, 1924), even though no demonstrable change in the size of the heart can be seen in x-ray photographs If there is increase in contraction and no decrease in size of the heart the experiments which are now reported permit the inference that cardiac output increases This may be the situation in heart failure in man, but of this there is no direct evidence Should the mechanism of heart failure involve decrease in the volume output, as has until recently been generally believed to be the case, point would be given to what Starling (1918) described as the law of the heart Starling believed, and showed in experiments, that when heart muscle fibers increased beyond a certain optimal length, decrease in output from the heart resulted If the optimal, or a somewhat shorter length, were restored, output from the ventricles mounted Heart failure may be a condition in which the fibers are longer than optimal, were digitalis able to restore them to a proper length, the requirement of the situation would be met We have no information that contributes to an elucidation of this problem, but these considerations may explain why in the absence of heart failure, that is to say of edema, the results in our dogs so far as alterations in volume output are concerned are without specific value The condition in them is simply not that of heart failure, they cannot be expected therefore to illustrate the mechanism which obtains in that condition

SUMMARY

We have studied the effect of digitalis upon the cardiac output, cardiac size and ventricular contraction of dogs with enlarged hearts, but without signs of heart failure We have found in them, as in normal dogs, that

1 The size of the heart is decreased
2 The extent of ventricular contractions is increased

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the mean pulmonary blood velocity[2] According to the formula of G N Stewart (3), Q equals $\frac{V\,T}{60}$ where Q is the quantity of blood in the lungs, V is the minute volume flow of blood through the lungs, and T, the *mean* pulmonary blood velocity in seconds If two of the factors are known, the third can be calculated Were von Kries and Tigerstedt correct in their contention that the speed of the fastest particle as expressed by the "circulation time" is twice the mean velocity, substitution of the pulmonary circulation time for T, the mean velocity time, would result in magnifying Q, the quantity of blood in the lungs, which would then become twice too great If on the contrary, the pulmonary circulation time is an index of the mean velocity, the substitution should give a result which conforms to the results of animal experiments

Methods and Results

The crude pulmonary circulation time was measured according to the method previously described (5) The actual pulmonary circulation time, that is to say, the time interval between the arrival of the active deposit of radium in the pulmonary artery and its arrival in the left auricle was estimated by subtracting four seconds from the crude pulmonary circulation time Four seconds includes the time the active deposit consumes in passing through the heart and varies according to the phase of the cardiac cycle at which the active deposit enters this organ The four seconds also accounts for the time necessary for the active deposit to travel from the left ventricle to the antecubital arteries

The minute volume of pulmonary blood flow was measured by the gasometric method of Field, Bock, Gildea and Lathrop (6) Except in the first few subjects, six to nine "alveolar" and "virtual venous" gas samples were analyzed Occasional discrepant results due to evident errors of technique were discarded The respiratory minute volume was measured in all subjects, and in nine of the seventeen subjects, the respiratory quotient, and the total CO_2 elimination per minute were measured after, as well as before, the collection of the

[2] By this phrase is meant "the mean time occupied by the passage of blood through the lungs"

the mean pulmonary blood velocity[2] According to the formula of G N Stewart (3), Q equals $\frac{V\,T}{60}$ where Q is the quantity of blood in the lungs, V is the minute volume flow of blood through the lungs, and T, the *mean* pulmonary blood velocity in seconds If two of the factors are known, the third can be calculated Were von Kries and Tigerstedt correct in their contention that the speed of the fastest particle as expressed by the "circulation time" is twice the mean velocity, substitution of the pulmonary circulation time for T, the mean velocity time, would result in magnifying Q, the quantity of blood in the lungs, which would then become twice too great If on the contrary, the pulmonary circulation time is an index of the mean velocity, the substitution should give a result which conforms to the results of animal experiments

Methods and Results

The crude pulmonary circulation time was measured according to the method previously described (5) The actual pulmonary circulation time, that is to say, the time interval between the arrival of the active deposit of radium in the pulmonary artery and its arrival in the left auricle was estimated by subtracting four seconds from the crude pulmonary circulation time Four seconds includes the time the active deposit consumes in passing through the heart and varies according to the phase of the cardiac cycle at which the active deposit enters this organ The four seconds also accounts for the time necessary for the active deposit to travel from the left ventricle to the antecubital arteries

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TABLE 1

Measurement of the pulmonary blood velocity, the minute volume blood flow through the lungs, and the quantity of blood in the lungs

Number	Date	Age	Vital capacity	Vital capacity per square meter	Respiratory minute volume	Respiratory quotient	Alveolar CO_2 tension	Average alveolar CO_2 tension	'Virtual' venous CO_2 tension	Average "virtual" CO_2 tension	Difference arterial and venous CO_2 content	CO_2 elimination per minute	Circulation rate	Arm to heart circulation time	Crude pulmonary circulation time	Actual pulmonary circulation time	Amount blood in lungs	Weight of patient	Calculated blood volume	Total blood in lungs
	1927		*cc*	*cc*	*liters*		*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*cc*	*liters per minute*	*seconds*	*seconds*	*seconds*	*cc*	*kgm*	*cc*	*per cent*
1	February 2	17	4,300	2,690	10 5		6 06	6 05	6 87	7 02	2 60	220	8 5	5 5	9	5	750	51 0	3,920	19
							5 76		7 03											
							6 11		7 16											
							6 11													
							6 20													
2a	February 4	36	3,250	1,957	8 3		5 91	5 94	6 77	6 99	2 82	208	7 4	13	12	8	920	58 0	4,460	21
							5 89		6 90											
							5 96		7 08											
							5 98		7 20											
2b	February 5	36	3,250	1,957	8 6		5 78	5 72	6 91	6 88	3 16	205	6 5							
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7	February 23	21	4,900	2,662	8 9		5 72	5 63	6 54	6 64	2 76	308	11 1	8	12 5	8 5	1,558	68 9	5,300	29
							5 41		6 68											
							5 67		6 91											
							5 76		6 46											
							5 69		6 88											
							5 58		6 69											
							5 52		6 36											
							5 70		6 58											
8	February 26	21	4,100	2,611	6 4		6 18	6 20	7 24	7 14	2 31	159	6 9	5 5	11 5	7 5	864	53 4	4,108	21
							6 10		7 24											
							6 45		6 97											
							5 93		7 05											
							6 37		6 86											
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13	April 6	26	4,800	2,700	5 8	0 79	4 93	5 26	6 41	6 35	3 02	191	6 3	10	15	11	1,162	62 3	4,790	24
					5 9	0 78	5 57		6 46											
							5 16		6 57											
							5 16		6 13											
							5 21		6 33											
							5 87		6 48											
							5 09		6 20											
							5 12		6 36											
									6 22											
14	April 27	42	3,100	2,065	5 8	0 79	5 78	5 65	7 60	7 19	4 27	165	3 9	13	14	10	642	47 8	3,680	17
					6 1	0 85	5 77		6 56											
							5 60		7 71											
							5 79		7 56											
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in the formula they are used as an expression of conditions existing simultaneously The wide variation in the estimated quantity of blood in the lungs is, however, greater than the probable experimental error and suggests that the elasticity of the pulmonary tissue permits the accommodation of widely varying volumes of blood

On the basis of our data, and assuming that the total blood volume of man is one-thirteenth of the body weight, the percentage of the total blood in the lungs was calculated Wide variations were found in the amounts of blood in the lungs, the greater amounts were generally associated with slower blood flow The average amount of blood in the lungs was, as has been said, 21 per cent of the total blood volume No great weight is to be attached to the absolute values obtained though the results conform in general to those observed experimentally in animals G N Stewart (3) observed that when both sides of the heart were completely obstructed simultaneously, the lungs in two animals contained respectively 21 and 18 6 per cent of the total blood volume Similarly, Kuno (7), studying the heart lung preparation under various conditions found from 8 8 to 19 4 per cent of the total blood in the lungs In animals, by using the pulmonary circulation time as a measure of the mean velocity, Stewart found 11 to 24 per cent of the total blood in the lungs The average amount was 17 per cent

On the basis of the data presented in this communication the estimated amount of blood in the lungs in man conforms so closely to the experimental results of Kuno and Stewart as to indicate that the pulmonary circulation time is an index of the mean time of blood flow through the lungs

The fact that the pulmonary circulation time is such a close index of the mean time consumed by blood flow through the lungs, also indicates that "stringing out" effects caused by variations in the speed of blood flow through different pathways is not of great consequence in normal individuals, and that the different available pathways through the lungs are approximately equal

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tomatology Mason (14) reported similar results in a case of nephritis of the azotemic type In another communication (15) three cases of chronic nephrosis treated with parathyroid extract are reported from the clinical viewpoint The present communication concerns some observations on the calcium metabolism of two of these cases A summary of the history of these patients is appended

Case I I H, female, aged 4 Admitted in August, 1925, with general anasarca No history of previous infections, and apparently well until three days before admission, when edema first appeared in the feet, rapidly extending to involve the whole body

Physical examination Marked general anasarca, tonsils enlarged, not inflamed Sinuses negative Heart not enlarged Blood pressure 106/78 Liver just palpable beneath costal margin Fundi normal Urine—albumin 15 grams per liter, granular casts, leucocytes Specific gravity 1014–1022 Blood non-protein nitrogen 25 mgm per 100 cc Total protein 5 05 per cent Albumin globulin ratio 1 3 2 Cholesterol 425 mgm per 100 cc Calcium 5 7 mgm per 100 cc Wassermann negative Slight anemia

At the time the present observations were made there had been no appreciable change in the general condition for some six months in spite of various therapeutic procedures

Case II R F, male, age 20 Admitted in September, 1926, with general anasarca Was unaware of any renal disease until September, 1925, when life insurance was refused because of albuminuria No history of infections except "Grippe" Edema began in February, 1926, and had been increasing up to time of admission

Physical examination General anasarca, heart not enlarged Vessels not sclerosed Blood pressure 142/92 Fundi negative Urine—albumin 11 grams per liter, hyaline and granular casts Specific gravity varied from 1014–1018, nocturnal polyuria, specific gravity 1012 Urea concentration 1 48 per cent Factor 21.3 (MacLean) Blood urea nitrogen 20 7 mgm per 100 cc Calcium 8 7 mgm per 100 cc Blood proteins 5 49 per cent Albumin globulin ratio 1 2 Cholesterol 500 mgm per 100 cc Basal metabolic rate—30.4 per cent Wassermann negative

GENERAL METHODS

Each patient was supplied a weighed diet of general nature, the composition of which remained unchanged during the whole course of the experimental period In case I occasional portions of food not eaten at meal time were fed during the course of the day, in case II all the diet was eaten at meals Under these conditions the

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The urine was collected under toluol in 24-hour amounts starting at 6 a m , the completeness of collection was checked by daily creatinine determinations In case II these values were practically constant, in case I, where the daily values did not check, the daily averages for each complete period agreed closely This was apparently due to the fact that owing to incomplete emptying of the bladder at the end of each 24-hour period, the collections for these periods were incomplete, however, when collections were extended over five days, this error became minimized and a daily average was arrived at

At the beginning and end of each period 0 3 gram carmine was given by mouth at 6 a m , and all stools from the first appearance of the dye up to the appearance of the second dose were collected and included in that period The total resulting stool was evaporated on a water bath, dried to constant weight in an oven at 100°C , ground to a fine powder, and thoroughly mixed, aliquot portions of this powder were taken for the various analyses

Blood for calcium determination was drawn from the antecubital veins twelve hours after the administration of parathyroid extract, allowed to clot, and the serum separated as soon as possible by centrifugalization

CHEMICAL METHODS

Calcium in the serum was estimated by Fiske's modification of Kramer and Tisdall's method (17) The calcium in the urine was determined on volumes of 25 cc , evaporated to dryness, ashed in the muffle furnace at faint red heat, and made up to the original volume in solution in 0 1 N HCl Ten cubic centimeters of this solution was measured into a centrifuge tube, 4 cc of saturated solution of ammonium oxalate added, and the reaction then adjusted to the turning point of methyl red (approximately pH 5) by the addition of ammonium hydroxide The procedure was then carried out as for the serum

In the case of the stools, 1 gram of finely powdered dried feces was ashed and made up to 100 cc volume similarly to the urine The calcium in aliquot parts of this solution was then determined as above

All ashings and precipitations were carried out in duplicate, and only results which checked were accepted

DISCUSSION

The most striking feature is the extremely small amount of calcium excreted during the control period in the urine of these patients,

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and calcium lactate were given together, there was a definite increase approaching the minimum value found by Sherman (21) in normal children of similar age A like effect, however, was not obtained in case II, an adult

In the low urinary excretion of calcium these subjects resemble the subject of Bergeim, Stewart and Hawk (23), who after thyroparathyroidectomy, showed an average daily output of 9 3 mgm in the urine A similarly reduced excretion in children suffering from nephritis and from nephrosis has been reported by Boyd, Courtney and MacLachlan (22), and in several nephritics, apparently in uremic states, by Halverson, Mohler, and Bergeim (5)

In this connection the observations of Hetényi and Nógrádi (24) are of interest These authors found that after the intravenous injection of calcium salts, the excretion in the urine of nephritic subjects was much less than in normal controls, their subjects, however, like those of Halverson, appear to have been of the azotemic, rather than the nephrotic, type

On the other hand, Hunter and Aub (19) have shown that in cases of lead poisoning, with presumably normal renal function, there was a marked increase in the calcium excreted in the urine when parathyroid extract was administered, the increase averaging 83 per cent above that of the control period Greenwald and Gross (25) have demonstrated that dogs receiving daily doses of parathyroid extract showed a marked increase in calcium excretion, the greatest increase being in the urine, and to a lesser extent in the stool These various investigators used, over long periods of time, doses of approximately the same average size as those used in our subjects, and the increased excretion in the urine began almost simultaneously with the administration of parathyroid extract Our case I, a child weighing 17 kgm, including edema, received 50 units of Collip's extract daily, actually a much larger dose per kilogram of body weight than that administered in the cases of lead poisoning

It would therefore seem probable that in these cases of nephrosis there is a definite impairment of the ability of the kidney to excrete calcium, an impairment which is not overcome by the use of parathyroid extract, even when the level of calcium in the blood is raised to the normal

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the normal level of 10 2 mgm per cubic centimeter was reached after several days of parathyroid extract therapy, this was not maintained during the short course of calcium lactate alone which followed it, but when the extract was again administered, along with the extra calcium lactate, the same normal level was reached, to fall again with the discontinuance of all therapy

It is possibly of significance that in both cases increases in the serum calcium were associated with increased excretion in the feces

COMMENT

In view of the recent studies of Aub and Bauer (26), who have shown that in myxedema the excretion of calcium is less than in the normal individual, whereas in hyperthyroid states it is greater, it is of interest to note that in both of these patients the basal metabolic rate was much below normal (−20 to −30 per cent), a typical finding in nephrosis first pointed out by Epstein (27) It is possible that their low calcium excretion is due to a mechanism similar to that acting in the myxedema cases of Aub and Bauer (26) Unfortunately no studies of calcium excretion were made while these patients were under thyroid therapy

On the other hand, the observations of Greenwald and Gross (28) have shown that, in dogs, after the removal of the parathyroid glands along with the thyroid, there is a marked decrease in the excretion of calcium, rendering easy the maintenance of a positive balance, a low serum calcium is also a marked feature When parathyroid extract is given, however, these animals again resume a normal excretion

Though no actual determination was made of the calcium in the diet, yet if it be estimated even approximately according to Sherman's tables (16) it would appear that these patients with their low calcium excretion were always in positive calcium balance When the parathyroid extract was given, however, the excretion was increased, tending to decrease the positive balance The administration of moderately large doses of calcium lactate by mouth was more than sufficient to balance the increased excretion produced by the parathyroid extract

It is possible that it is a combined thyroid and parathyroid in-

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COMMENT

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On the other hand, the observations of Greenwald and Gross (28) have shown that, in dogs, after the removal of the parathyroid glands along with the thyroid, there is a marked decrease in the excretion of calcium, rendering easy the maintenance of a positive balance, a low serum calcium is also a marked feature When parathyroid extract is given, however, these animals again resume a normal excretion

Though no actual determination was made of the calcium in the diet, yet if it be estimated even approximately according to Sherman's tables (16) it would appear that these patients with their low calcium excretion were always in positive calcium balance When the parathyroid extract was given, however, the excretion was increased, tending to decrease the positive balance The administration of moderately large doses of calcium lactate by mouth was more than sufficient to balance the increased excretion produced by the parathyroid extract

It is possible that it is a combined thyroid and parathyroid in-

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10 Keith, N M , Barrier, C W , and Whelan, M , Jour Amer Med Assoc , 1924, lxxxiii, 666 Treatment of Nephritis and Edema with Calcium
11 Salvesen, H A , Hastings, A B , and MacIntosh, J , Jour Biol Chem , 1924, lx, 327 The Effect of the Administration of Calcium Salts on the Inorganic Composition of the Blood
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14 Mason, E H , Can Med Assoc Jour , 1926, xvi, 538 A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract
15 Lewis, D S , and Scriver, W de M , Annals of Int Med , (in press) The Response of Chronic Nephrosis to Parathyroid and Thyroid Medication
16 Sherman, H C , 1924, Chemistry of Food and Nutrition, Macmillan & Co , p 421
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23 Bergeim, O , Stewart, F T , and Hawk, P B , Jour Exper Med , 1914, xx, 218 A Study of the Metabolism of Calcium, Magnesium, Sulphur, Phosphorus, and Nitrogen in Acromegaly
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glomerular nephritis with marked renal injury changes also occur as a result both of retention of acid (chiefly phosphoric and sulfuric, occasionally also hydrochloric) and loss of plasma fixed base, dependent primarily upon the failure of the kidney to excrete acid neutralized by ammonia and secondarily upon a failure of the kidney to secrete urine of the normal maximum acidity, (3) that as total electrolyte diminishes in the plasma, non-protein nitrogen increases so that the osmotic pressure remains normal, (4) that consequently, the alteration in the concentration and composition of plasma electrolyte and not the concentration of non-protein nitrogen should be considered as the more important result of renal insufficiency

The chemical methods were the same as described previously (2) In an attempt to calculate the equivalent *osmolar* concentration of the individual electrolytes and non-electrolyte crystalloids from their molar concentration, advantage was taken of the following facts and assumptions

(1) According to Landolt and Bornstein (4), the molecular lowering of the freezing point of NaCl is 3 45°C , which would make the osmolar concentration by volume 1 87 times the molar

(2) According to the same authors, the molecular lowering of the freezing point of $NaHCO_3$ is 3 59°C which would make its osmolar concentration by volume 1 95 times the molar

(3) The molecular lowerings, according to the same authors, of Na_2HPO_4 and NaH_2PO_4 are 5 0°C and 3 59°C, respectively If we assume that the ratio Na_2HPO_4/NaH_2PO_4 remains 4/1, the osmolar concentration by volume of the serum inorganic phosphate can be calculated by multiplying the concentration of inorganic phosphate in mgm per cent by the factor 1 02

(4) The osmotic effect of the protein we considered as being equivalent to that of undissociated B-protein (calculated by Van Slyke's (5) formula for human blood)

(5) Lactic acid was considered as being present in the form of Na lactate, with the same degree of dissociation as NaCl Its osmolar concentration by volume, therefore, would be 1 87 times its molar

(6) The osmotic effect of non-protein nitrogen was assumed to be due entirely to urea and was calculated on the assumption that 70 per cent of the non-protein nitrogen was urea nitrogen The remainder was not taken into account

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ACUTE HEMORRHAGIC NEPHRITIS

Protocols

Cases 1 to 16, inclusive These cases were typical uncomplicated cases of acute hemorrhagic nephritis, without uremia, marked edema, or marked vomiting

Case 17 Cletus B Age, 9 years This patient was admitted on May 12, 1927 Three weeks previously edema was noted, which steadily increased He complained of headache, nausea, vomited occasionally and during the night before admission had two generalized convulsions When admitted he was quite drowsy There was general anasarca His blood pressure was 187/100 mm Hg There was moderate fever and leucocytosis The mucous membrane of his nose was reddened, particularly over the left middle turbinate The tonsils were enlarged and red Frequent convulsions occurred during the first twenty-four hours, despite the free use of sedatives A very small amount of urine, containing many red blood cells, leucocytes and casts was passed during this period Two hundred fifty cubic centimeters of 20 per cent glucose were given intravenously, and there followed a very marked improvement Convulsions ceased, diuresis occurred, edema was rapidly lost, the urine cleared and on May 17 when the patient left the hospital there was only a faint albuminuria

Case 18 Rose M Age, 14 years This patient had been well until about two weeks before hospital admission on March 28, 1928 She then became ill with fever, cough and headache A week later edema of her face, feet and abdomen were noted This edema largely subsided after about four or five days Her urine was not examined during that time On March 27 three generalized convulsions occurred, each lasting several minutes When first seen at the hospital she was without edema, fever or other signs of acute infection, but much disoriented Her blood pressure was 162/108 mm Hg Her urine showed considerable albumin and many red blood cells, white blood cells and casts Two more generalized convulsions occurred before blood was taken for chemical examination One hundred forty cubic centimeters of 1 per cent magnesium sulfate solution were then given intravenously, after which she became quiet and had no more convulsions The blood pressure gradually returned to normal by April 5 On April 14 the urine was free from albumin and blood cells and showed but an occasional cast and the patient was discharged

Case 19 Tom F Age, 5 years Except for frequent colds, this patient was well until about October 8, 1926, when edema of the eyelids was noted A few days later, the scrotum became edematous, and on October 20 he was admitted to the hospital He then had generalized edema and ascites The urine contained a large amount of albumin and many leucocytes and red blood cells His tonsils and adenoids were hypertrophied and infected, pus was present in the nose and

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TABLE 1

The composition of the blood serum in cases of acute hemorrhagic nephritis

Case	Date	NaCl	CO_2 content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N*	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
Typical uncomplicated cases (1–16 inclusive)																
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm. per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Maximum value		638	65.5	7.48	9.56	8.4	14.1	27.7	148	86.0	149	148	8.0	307	337	
Minimum value		503	34.5	7.35	5.47	2.0	9.5	11.3	58	25.0	140	134	−3.0	273	280	
Average value		569	53.0	7.39	7.12	5.6	11.0	22.1	104	45.7	144	141	2.7	291	310	
Number of determinations		26	25	23	26	17	8	16	23	26	11	15	11	15	5	
Cases with acute uremic convulsions																
Cletus B No 17	May 12 1927	623	28.1	7.13	6.55	4.2		110	223	43.3	139	145	−6.0	307		Marked edema and elevation of blood pressure Urine strongly acid Ammonia present in large amount
	May 13, 1927	591	40.2	7.39	6.55	5.9	12.4	36.7	130	58.3		139		292		
Rose M No 18	March 29, 1928	597	48.7	7.32	7.20	4.6		40.3	109	29.0	163	144	19.0	293		No edema Blood pressure elevated
Cases with marked oliguria and edema																
Tommie F No 19	October 23 1926	562	54.9	7.37	5.03	5.9	9.3		82	36.3						Marked edema
	October 25 1926	561	48.9	7.35	5.25	(5.9)		39.2		38.3	137	135	2.0	278		
	November 2 1926	567	56.1	7.40	6.34		9.1		87	32.3						Moderate edema
	November 8 1926	585	46.7	7.36	6.34											

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Maximum value		638	65 5	7 48	9 56	8 4	14 1	27 7	148	86 0	149	148	8 0	307	337	
Minimum value		503	34 5	7 35	5 47	2 0	9 5	11 3	58	25 0	140	134	−3 0	273	280	
Average value		569	53 0	7 39	7 12	5 6	11 0	22 1	104	45 7	144	141	2 7	291	310	
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blood are shown in table 1 and chart 1 During the next five days, there was irregular fever, the temperature fluctuating from 37°C to 39 3°C The leucocyte count rose from 10,800 on admission to 21,000 on April 14 Persistent vomiting continued On April 14, both antra were irrigated, pus being washed out, and the left mastoid was opened, pus also being found From both the mastoid and the blood stream *Streptococcus hemolyticus* was cultured Following mastoidectomy vomiting ceased immediately A marked skin eruption of the erythema multiforme type appeared The patient's condition steadily improved, despite the fact that the septicemia persisted until April 20 and that an abscess, probably embolic, developed in the chest wall Following tonsillectomy and adenoidectomy on May 21, fever and gross hematuria recurred, lasting for a week The maxillary antra were treated by repeated irrigations The patient was then sent to the country department of the hospital for convalescence There her temperature became normal, her urine cleared completely, and she gained 30 pounds in weight in 9 months

Therapy directly influencing the composition of the blood studied was as follows On April 12, after the first blood sample was obtained, 900 cc of Ringer's solution were given intraperitoneally, and 400 cc of 10 to 20 per cent glucose intravenously After the second blood sample on the same day, 1500 cc of Ringer's solution and 100 cc of glucose were given On April 14, 400 cc of Ringer's solution were given intraperitoneally and 250 cc of glucose solution intravenously On April 15, 175 cc of blood, and on April 21, 180 cc of blood were given intravenously

Case 22 Luella R Age, 5 years This patient was admitted on December 3, 1921 A month previously, she had complained of earache and had fever A week before admission there was a spontaneous rupture of one ear drum Hematuria and marked vomiting were present for three days before admission On admission, the patient was desiccated and had slight fever The urine contained gross blood, much albumin and many casts The tonsils were large and ragged and the left ear was discharging pus through a good sized perforation With rest in bed and restricted diet, the general condition improved, the urine cleared, and on April 22 the tonsils and adenoids were removed

Case 23 Tommie M Age, 6 years This patient had been well until he was injured during a tornado in the latter part of September, 1927 He received many skin wounds, which later became infected About the first of November, blood was noted in his urine, slight fever was present and vomiting became very marked A week later, November 8, 1927, he was admitted to the hospital He was found to be undernourished and with several infected skin wounds and many scars of wounds already healed The tonsils were ragged and red and there was considerable pus seen in his nose His urine showed gross blood and a large amount of albumin With rest in bed and restricted diet, his urine gradually cleared and became negative on December 12, at which time he was discharged on a regular diet.

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22 1 Glucose varied from 58 to 148 mgm per cent Total base varied only from 140 to 149, averaging 144 mM "Total" acid (Cl + HCO_3 + protein + HPO_4 + lactic acid) varied somewhat more, from 134 to 148 mM, averaging 141 Undetermined acid varied from −3 0 to 8 0, averaging 2 7 mM By freezing point determinations, in five instances the osmotic pressure averaged 310 mM, varying between 280 and 337 The calculated osmotic pressure varied from 273 to 307, averaging 291 mM, or 94 0 per cent of the average determined osmotic pressure, a normal relationship Non-protein nitrogen varied from 25 to 86 mgm per cent, averaging 45 7

Cases with acute uremic convulsions

Case 17, whose blood was studied shortly after uremic convulsions had occurred, showed a marked "acidosis" The $BHCO_3$ content was reduced by 11 mM and was almost exactly equalled by the 10 2 mM increase in lactic acid The pH had dropped to 7 13 BCl was increased by 7 mM There was also hyperglycemia, the glucose content being 223 mgm per cent On the next day, with cessation of convulsions, there was noted an increase in $BHCO_3$ of 5 1 mM with a decrease of 8 1 mM lactic acid and 6 mM BCl As calculated, about 6 mM electrolyte had left the blood stream Diuresis had not yet begun, and edema was apparently increasing during this period The lactic acid "acidosis" in this instance undoubtedly occurred as a result of the convulsions and anoxemia present at and before the time that the blood was studied

Case 18 was a similar case and similarly showed decrease in $BHCO_3$ and increase in lactic acid An unusually high value for undetermined acid, 19 0 mM, was indicated, however Total base in this instance was unusually high, and may have been in error, and such a large quantity of undetermined acid may not really have existed

It is rather interesting to note that in Case 17 the non-protein nitrogen during the acute uremic manifestations was but 43 3 mgm per cent, and in Case 18 but 29 mgm per cent

Cases with marked oliguria and edema

Case 19, when admitted was at first mistaken for nephrosis Edema and albuminuria were very marked, and there was neither non-protein

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as well as non-protein nitrogen was noted On November 29, however, a few days after a decided diuresis with loss of edema fluid had begun, an interesting chemical picture was noted $BHCO_3$ was still reduced, but BCl was decidedly higher than normal Total acid was slightly above the normal and non-protein nitrogen had dropped almost to the normal value A normal freezing point at this time was observed and agreed well with the calculated one

Cases with marked vomiting and dehydration

Case 21 was admitted after two weeks of marked vomiting and one week of hematuria, the results of a hemolytic streptococcic infection of one mastoid and both maxillary antra Severe dehydration was present The blood picture on admission was extremely interesting BCl was greatly reduced, being but 71 mM $BHCO_3$ was of a low normal concentration, 21 0 mM The pH was 7 35 Protein concentration was 7 96 per cent, as compared with 5 24 per cent following restoration of a normal fluid balance, thus indicating marked water loss from the plasma Inorganic phosphate was very much increased and calcium considerably decreased Total base was also considerably reduced, 127 mM , and exceeded "total" acid by 7 0 mM The undetermined acids were presumably sulfuric and lactic The total electrolyte osmolar concentration as calculated was only 227 mM Non-protein nitrogen, however, was so elevated (250 mgm per cent) that the *total* osmolar concentration as calculated was 301 mM in very good agreement with the observed freezing point indicating a concentration of 308 mM The administration of 900 cc of Ringer's solution and 400 cc of 10 per cent glucose on the day of admission effected a considerable dilution of the plasma, judging from the fall of plasma protein from 7 96 to 7 03 per cent, but vomiting persisted and BCl remained low, while $BHCO_3$ increased to 28 1 mM Inorganic phosphate reached the enormous value of 24 5 mgm per cent, and calcium the low value of 3 6 mgm per cent The total electrolyte osmolar concentration was little altered, being but 230 mM and the non-protein nitrogen remained elevated As before, the freezing point indicated a normal osmotic pressure (309 mM)

With further administration of Ringer's solution, there occurred an increase in BCl to 810 mM on April 14 sufficient to raise the elec-

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With further administration of Ringer's solution, there occurred an increase in BCl to 810 mM on April 14 sufficient to raise the elec-

TABLE 2

The composition of the blood serum in cases of sub acute and chronic glomerular nephritis

Case	Date		NaCl	CO₂ content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N *	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
			mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm. per cent*	*mgm per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Elizabeth Z. No 24	January	12, 1925	597	(50 0)	(7 40)	5 03	(6 0)		(18 0)	110	71 0		140		297		Moderate edema and elevation of blood pressure Urine strongly acid, containing chloride and ammonia
	April	8 1925	585	(50 0)	(7 40)	5 25	(6 0)		(18 0)		44 0		138		282		No edema Blood pressure 130/80
	April	9, 1925	516	(40 0)	(7 35)	3 50	(9 0)		(18 0)		57 0		123		261		Slight edema Blood pressure 88/40
	April	11, 1925	480	14 2	(7 20)	5 25	13 2		(18 0)		89 0		108		234		Marked edema Blood pressure 90/60
	April	13, 1925	471	35 3	(7 30)	5 47	14 4		(18 0)		152		116		268		Marked edema Blood pressure 110/82
	April	14, 1925	456	42 4	(7 35)	6 58	12 0		(18 0)		191		119		288		No edema
	April	14, 1925	517	38 1	(7 35)	6 12	14 4		(18 0)		200		127		300		Urine from April 11 to May 11 contained but very little chloride or ammonia and was strongly acid
	April	15, 1925	512	38 3	(7 35)	6 12	10 8		(18 0)		225		125		304		
	April	18, 1925	514	40 6	(7 35)	6 12	11 6		(18 0)		190		125		297		
	April	20 1925	512	(41 0)	(7 35)	(6 23)	(10 0)		(18 0)		112		126		275		
	April	23 1925	527	(41 0)	(7 35)	6 34	(10 0)		(18 0)		102		128		279		
	April	27, 1925	519	(41 0)	(7 35)	8 49	(8 0)		(18 0)		99 0		130		282		
	April	29, 1925	505	43 0	(7 35)	(8 06)	(8 0)		(18 0)		66 0		128		267		Very slight edema Blood pressure 136/112
	May	3, 1925	521	44 3	(7 35)	(7 63)	(8 0)		(18 0)		96 0		130		282		
	May	8, 1925	479	39 6	(7 35)	7 20	(8 0)		(18 0)		82 0		130		258		
	May	11 1925	468	33 0	(7 35)	6 98	(8 0)		(18 0)		89 0		117		251		
	May	16 1925	527	(45 5)	(7 35)	7 55	7 6		(18 0)		72 0		129		271		

TABLE 2

The composition of the blood serum in cases of sub acute and chronic glomerular nephritis

Case	Date	NaCl	CO_2 content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N*	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm. per cent*	*mgm per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Elizabeth Z. No 24	January 12, 1925	597	(50 0)	(7 40)	5 03	(6 0)		(18 0)	110	71 0		140		297		Moderate edema and elevation of blood pressure Urine strongly acid, containing chloride and ammonia
	April 8 1925	585	(50 0)	(7 40)	5 25	(6 0)		(18 0)		44 0		138		282		No edema Blood pressure 130/80
	April 9, 1925	516	(40 0)	(7 35)	3 50	(9 0)		(18 0)		57 0		123		261		Slight edema Blood pressure 88/40
	April 11, 1925	480	14 2	(7 20)	5 25	13 2		(18 0)		89 0		108		234		Marked edema Blood pressure 90/60
	April 13, 1925	471	35 3	(7 30)	5 47	14 4		(18 0)		152		116		268		Marked edema Blood pressure 110/82
	April 14, 1925	456	42 4	(7 35)	6 58	12 0		(18 0)		191		119		288		No edema
	April 14, 1925	517	38 1	(7 35)	6 12	14 4		(18 0)		200		127		300		Urine from April 11 to May 11 contained but very little chloride or ammonia and was strongly acid
	April 15, 1925	512	38 3	(7 35)	6 12	10 8		(18 0)		225		125		304		
	April 18, 1925	514	40 6	(7 35)	6 12	11 6		(18 0)		190		125		297		
	April 20 1925	512	(41 0)	(7 35)	(6 23)	(10 0)		(18 0)		112		126		275		
	April 23 1925	527	(41 0)	(7 35)	6 34	(10 0)		(18 0)		102		128		279		
	April 27, 1925	519	(41 0)	(7 35)	8 49	(8 0)		(18 0)		99 0		130		282		
	April 29, 1925	505	43 0	(7 35)	(8 06)	(8 0)		(18 0)		66 0		128		267		Very slight edema Blood pressure 136/112
	May 3, 1925	521	44 3	(7 35)	(7 63)	(8 0)		(18 0)		96 0		130		282		
	May 8, 1925	479	39 6	(7 35)	7 20	(8 0)		(18 0)		82 0		130		258		
	May 11 1925	468	33 0	(7 35)	6 98	(8 0)		(18 0)		89 0		117		251		
	May 16 1925	527	(45 5)	(7 35)	7 55	7 6		(18 0)		72 0		129		271		

TABLE 2—*Continued*

Case	Date	NaCl	CO_2 content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N*	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Marie H No 26	November 3, 1925	608	31.8	7.10	8.06	9.5	6.8	(18.0)	70	170		139		321		
	November 9, 1925	614	32.4	7.35	7.85	9.5		(18.0)	84	130		142		313		
	November 17, 1925	620	32.0	7.30	8.19	(9.5)	6.0	(18.0)	82	111		144		311		
	November 25 1925	550	31.6	(7.30)	6.66	(9.5)	8.3	(18.0)	106	117		129		285		
	December 31, 1925	620	23.4	(7.30)	6.67	(9.5)	6.6	(18.0)		108		138		299		
	January 1, 1926	585	19.9				8.6	(18.0)		107						
	January 5, 1926	491	22.5	7.28	7.44		8.6		111	160						
	January 8, 1926	725	21.6	7.25	6.83	11.0	9.0	(18.0)	112	170		150		347		
	January 11, 1926	608	20.0	7.27	7.20	13.4	6.6	(18.0)	109	180		133		320		
	January 25, 1926	562	28.3	(7.27)	6.55			(18.0)	109	163						
	February 3, 1926	562	32.5	7.27	8.28	13.6		(18.0)	122	60.0		132		284		
	February 12, 1926	596	36.3	7.20	8.05		6.6		96	146						
	March 18, 1926	602	43.7	7.36	5.47	11.3	6.0	(18.0)	112	67.0		140		292		
	April 12, 1926	591	33.2	7.23	6.25		7.2		130	112		133		300		
	May 17, 1926	661	28.5	(7.25)	5.57	12.6			103	101						
	June 14, 1926	649	33.5	7.30	5.47				122	99.0						
	July 12 1925	670	34.7	7.32	5.25		6.9		112	87.0	145	132	13	289		
	August 9, 1926	573	31.8	7.38	5.68	4.5	7.3	(18.0)	109	123		136		285		
	August 23, 1926	655	29.0	(7.35)	5.47	7.2				92.0						
	August 25, 1926	612	32.6	7.35	5.03	6.5	6.6	(18.0)				131				
	August 29, 1926	616	34.8	7.35	5.25				142	108	146					
	September 6 1926	619	35.8	7.37	4.48		7.9		96	96.0						
	September 14, 1926	608	29.1	7.35	5.47	4.0				95.0	145	128	7	289		

TABLE 2—*Continued*

Case	Date	NaCl	CO2 content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N*	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Marie H No 26	November 3, 1925	608	31 8	7 10	8 06	9 5	6 8	(18 0)	70	170		139		321		
	November 9, 1925	614	32 4	7 35	7 85	9 5		(18 0)	84	130		142		313		
	November 17, 1925	620	32 0	7 30	8 19	(9 5)	6 0	(18 0)	82	111		144		311		
	November 25 1925	550	31 6	(7 30)	6 66	(9 5)	8 3	(18 0)	106	117		129		285		
	December 31, 1925	620	23 4	(7 30)	6 67	(9 5)	6 6	(18 0)		108		138		299		
	January 1, 1926	585	19 9				8 6	(18 0)		107						
	January 5, 1926	491	22 5	7 28	7 44		8 6		111	160						
	January 8, 1926	725	21 6	7 25	6 83	11 0	9 0	(18 0)	112	170		150		347		
	January 11, 1926	608	20 0	7 27	7 20	13 4	6 6	(18 0)	109	180		133		320		
	January 25, 1926	562	28 3	(7 27)	6 55			(18 0)	109	163						
	February 3, 1926	562	32 5	7 27	8 28	13 6		(18 0)	122	60 0		132		284		
	February 12, 1926	596	36 3	7 20	8 05		6 6		96	146						
	March 18, 1926	602	43 7	7 36	5 47	11 3	6 0	(18 0)	112	67 0		140		292		
	April 12, 1926	591	33 2	7 23	6 25		7 2		130	112		133		300		
	May 17, 1926	661	28 5	(7 25)	5 57	12 6			103	101						
	June 14, 1926	649	33 5	7 30	5 47				122	99 0						
	July 12 1925	670	34 7	7 32	5 25		6 9		112	87 0	145	132	13	289		
	August 9, 1926	573	31 8	7 38	5 68	4 5	7 3	(18 0)	109	123		136		285		
	August 23, 1926	655	29 0	(7 35)	5 47	7 2				92 0						
	August 25, 1926	612	32 6	7 35	5 03	6 5	6 6	(18 0)				131				
	August 29, 1926	616	34 8	7 35	5 25				142	108	146					
	September 6 1926	619	35 8	7 37	4 48		7 9		96	96 0						
	September 14, 1926	608	29 1	7 35	5 47	4 0				95 0	145	128	7	289		

TABLE 2—*Concluded*

Case	Date	NaCl	CO_2 content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N*	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm. per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
Margaret Q No 31	January 4, 1928	620	44 1	7 27	4 16	9 0		65 6^{s}	96^{s}	47 0^{s}	139	145		297	311	Very marked edema Blood pressure elevated Urine pH 6+ Small amounts of ammonia, but considerable chloride
	January 6 1928	626	43 0	7 45	3 31	8 0		21 4^{s}	94^{s}	65 5^{s}	137	139		284	310	
	January 11, 1928	585	41 9	7 43	4 59	6 7		32 8^{s}	115^{s}	74 0^{s}		135		283		
	January 23 1928	626	53 0	7 43	4 16	7 0	9 4	17 6^{s}	103^{s}	53 0^{s}	154			297		
	February 10, 1928	608	51 2	7 41	4 59	7 9	8 5	13 9^{s}	112^{s}	68 5^{s}				298	328	
Mr T No 35	December 14, 1926	585	49 0	7 35	7 85	6 4	9 9	13 3		105		142		320		
Mr T No 36	January 7, 1928	538	34 8	7 35	7 63	10 0		47 8^{s}	160	120		134		297	322	No edema Blood pressure normal Urine pH 6+ Very little ammonia but considerable chloride
	January 10, 1928	503	34 1	7 29	8 06	6 3		25 2^{s}	126	134	140	123	17	278	307	
	January 12 1928	519	35 5	7 27	8 92	8 9	11 7	27 7^{s}		140	143	130	13	295	325	
	January 16, 1928	509	48 5	7 42	6 98	7 2	11 8	26 5^{s}	137	113	138	130	8	286	324	
	January 26 1928	509	68 0	7 28?	7 42	8 5	10 0	39 1^{s}	110	90 7	150	140	10	291	328	
	February 1, 1928	538	60 0	7 40	7 20	5 0			85	67 0	143	139	5	294	340	

* Whole blood determined except where serum determinations are indicated by postscript (s)
( ) indicates assumed values.
† N B The inorganic sulfate concentration of 10 0 mM is included

TABLE 2—*Concluded*

Case	Date	NaCl	CO₂ content	pH	Protein	Inorganic P	Ca	Lactic acid*	Glucose*	N P N *	Total base	Total determined acid	Undetermined acid	Calculated osmotic pressure	Observed osmotic pressure	Remarks
		mgm per cent	*volumes per cent*		*per cent*	*mgm per cent*	*mgm per cent*	*mgm per cent*	*mgm. per cent*	*mgm per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	
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	January 11, 1928	585	41 9	7 43	4 59	6 7		32 8^{s}	115^{s}	74 0^{s}		135		283		
	January 23 1928	626	53 0	7 43	4 16	7 0	9 4	17 6^{s}	103^{s}	53 0^{s}	154			297		
	February 10, 1928	608	51 2	7 41	4 59	7 9	8 5	13 9^{s}	112^{s}	68 5^{s}				298	328	
Mr T No 35	December 14, 1926	585	49 0	7 35	7 85	6 4	9 9	13 3		105		142		320		
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No 36	January 10, 1928	503	34 1	7 29	8 06	6 3		25 2^{s}	126	134	140	123	17	278	307	
	January 12 1928	519	35 5	7 27	8 92	8 9	11 7	27 7^{s}		140	143	130	13	295	325	
	January 16, 1928	509	48 5	7 42	6 98	7 2	11 8	26 5^{s}	137	113	138	130	8	286	324	
	January 26 1928	509	68 0	7 28?	7 42	8 5	10 0	39 1^{s}	110	90 7	150	140	10	291	328	
	February 1, 1928	538	60 0	7 40	7 20	5 0			85	67 0	143	139	5	294	340	

* Whole blood determined except where serum determinations are indicated by postscript (s)
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pH of approximately 6 5 and with but 2 to 3 mgm ammonia nitrogen per 100 cc A considerable amount of albumin was present, and the sediment was composed chiefly of granular casts and white blood cells There were occasional hyalin casts The Mosenthal test showed fixation of the specific gravity between 1 001 and 1 004 The concentration of non-protein nitrogen was never more than 240 mgm per cent The concentration of chloride varied between 53 mgm and 99 5 mgm per cent NaCl The phenolsulphonephthalein output was 19 per cent in 2 hours

Polydypsia remained marked and all urine was as described above Intramuscular injection of pituitrin had no effect on the concentration of the urine With a high caloric diet, largely milk, she gained weight rapidly Because of the diminished CO_2 content of the blood (see table 2), large amounts of orange juice, as an additional source of alkali, were given

Case 32 Woodrow W Age, 9 years Diagnosis Acute hemorrhagic nephritis when first seen which progressed into fatal chronic nephritis

Case 33 Davis B Age, 13 years Findings were those of chronic nephritis with hypertension (blood pressure 210/160) and myocardial damage

Case 34 Margaret Q Age, 12 years Diagnosis chronic nephritis with edema and hypertension

Cases 35 and 36 These cases were male adults showing evidence of renal insufficiency associated with prostatic hypertrophy They are included because of the rather complete blood data which we were able to obtain from them and because they seemed in many respects like the children studied with marked renal insufficiency

Cases of subacute and chronic glomerular nephritis

When acute glomerular nephritis is not completely recovered from, fibrous tissue replacement of kidney substance involving chiefly the glomeruli results Autopsy of cases of severe chronic nephritis with evidence of marked renal insufficiency frequently shows very little normal secreting tissue remaining It is, therefore, natural to assume that the chemical blood picture of severe chronic nephritis is the result of inadequate urinary secretion It did not seem correct to us, however, to look upon non-protein nitrogen increase in the blood as conclusive evidence of renal insufficiency in cases of acute glomerular nephritis, and the data from the following cases of subacute and chronic nephritis make us feel that non-protein nitrogen increase in

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the blood has the same significance that it has in acute nephritis In subacute or chronic nephritis, exacerbation of infection which provokes vomiting, diarrhea, or edema may have the same marked effect in lowering the electrolyte content of the blood and raising the non-protein nitrogen that it has in acute nephritis In the absence of acute infection, however, the same result may occur more gradually, because of faulty urinary secretion which permits electrolyte to be lost from the blood

Results of acute infection in sub-acute or chronic nephritis

When a severe exacerbation of infection in the form of paranasal sinusitis and septicemia by a hemolytic streptococcus occurred in case 24, on April 8, 1925, there followed a sudden appreciable reduction in concentration of serum chloride and bicarbonate (table 2, chart 2) If our single determination was correct, protein also suffered a transient but marked fall in concentration [1] At the same time, edema appeared Even in the absence of lactic acid and total base determinations, it seems certain that, as calculated, the osmotic pressure due to electrolyte suddenly diminished to a very marked degree, as calculated from 264 mM osmolar to 204 mM, a diminution of 22 8 per cent Coincident with the fall in BCl and $BHCO_3$, non-protein nitrogen and phosphate increased in the blood, so that the total calculated osmolar concentration dropped somewhat less (17 per cent) than that of the electrolyte alone On April 14, although the osmolar concentration of electrolyte was still much reduced, the total theoretical osmolar concentration was slightly higher than normal, due largely to increase in non-protein nitrogen Edema had disappeared by this time During the next few days, when the total osmolar concentration exceeded slightly the normal,[2] the reverse of edema, desiccation, was noted Gradually, however, electrolyte

[1] The low plasma protein value on April 9th, however, is questionable, since determinations a short time previously and subsequently agreed well with each other and were both considerably higher than the value in question

[2] As in case 21, the theoretical osmotic pressure was probably greater than the actual value when the non-protein nitrogen reached a very high level In all probability, the non-protein nitrogen did not overcompensate osmotically for loss of electrolyte as much as our calculation would indicate

the blood has the same significance that it has in acute nephritis In subacute or chronic nephritis, exacerbation of infection which provokes vomiting, diarrhea, or edema may have the same marked effect in lowering the electrolyte content of the blood and raising the non-protein nitrogen that it has in acute nephritis In the absence of acute infection, however, the same result may occur more gradually, because of faulty urinary secretion which permits electrolyte to be lost from the blood

Results of acute infection in sub-acute or chronic nephritis

When a severe exacerbation of infection in the form of paranasal sinusitis and septicemia by a hemolytic streptococcus occurred in case 24, on April 8, 1925, there followed a sudden appreciable reduction in concentration of serum chloride and bicarbonate (table 2, chart 2) If our single determination was correct, protein also suffered a transient but marked fall in concentration [1] At the same time, edema appeared Even in the absence of lactic acid and total base determinations, it seems certain that, as calculated, the osmotic pressure due to electrolyte suddenly diminished to a very marked degree, as calculated from 264 mM osmolar to 204 mM , a diminution of 22 8 per cent Coincident with the fall in BCl and $BHCO_3$, non-protein nitrogen and phosphate increased in the blood, so that the total calculated osmolar concentration dropped somewhat less (17 per cent) than that of the electrolyte alone On April 14, although the osmolar concentration of electrolyte was still much reduced, the total theoretical osmolar concentration was slightly higher than normal, due largely to increase in non-protein nitrogen Edema had disappeared by this time During the next few days, when the total osmolar concentration exceeded slightly the normal,[2] the reverse of edema, desiccation, was noted Gradually, however, electrolyte

[1] The low plasma protein value on April 9th, however, is questionable, since determinations a short time previously and subsequently agreed well with each other and were both considerably higher than the value in question

[2] As in case 21, the theoretical osmotic pressure was probably greater than the actual value when the non-protein nitrogen reached a very high level In all probability, the non-protein nitrogen did not overcompensate osmotically for loss of electrolyte as much as our calculation would indicate

found to be the equivalent of 10 mM univalent base We are inclined to believe, therefore, that in other instances in which undetermined acid seemed unusually large, as for instance cases 26, 28, 30, and 36, sulfuric acid was in all probability chiefly responsible

In different types of nephritis, Straub studied the blood from an acid-base viewpoint by determining individually the base ions, Na, K, and Ca and the principle acid ions, Cl′ and HCO_3' He did not determine phosphoric, sulfuric, or lactic acid, and did not attempt to calculate the base-binding capacity of the protein He did, however, besides determining the non-protein nitrogen, determine the actual freezing point and the electrical conductivity of the serum He frequently found, as did later Bulger and Peters and ourselves, considerable variations in Cl′ and HCO_3' ions, usually but not always in opposite directions Total base (Na + K + Ca) he found sometimes normal, but occasionally below or above normal He also occasionally found an unusual excess of "total" base over the sum of Cl′ and HCO_3' ions This difference in some cases he did not believe due to phosphoric, sulfuric or proteic acid, but to some unknown pathological acid This type of substance, together with a theoretical non-electrolyte (not non-protein nitrogen) constituted what he termed "mol-rest," that is, the difference between the calculat[illegible] and the observed osmotic pressure in millimoles [illegible]od,

Recalculating his most complete data as we [illegible] wha[illegible]lculated ours, we find the difference between "total" acid and t[illegible] base no greater than indicated by our data, and very little undetermined osmotically active substances except in one case (no 7 on July 23, 1923) In this instance, the total base found was 61 mM greater than the sum of the principal normal acids (Cl′ + HCO_3' + protein′) This is the only instance in which there was such a marked discrepancy between base and acid In this case we should have expected very high values for phosphate and sulfate, together perhaps binding 25 to 30 mM univalent base In addition, if marked circulatory failure had existed (as it very well might so shortly before death) lactic acid might have accounted for 10 to 15 mM more base By accumulation of these three acids, therefore, 35 to 45 mM of the 61 might have been accounted for In such an event, no very great amount of unusual acid needs to have been present If we calculate the total

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ammonia for fixed base was noted, and cases 31, 32 and 36 also showed inability to practice base economy by excreting urine of maximum acidity

Such inability of the damaged kidney to practice base economy has been demonstrated experimentally by Begun and Munzer (11), Beckman (12) and Linder (13) in a more direct manner After hydrochloric acid feeding in normal subjects and nephritics, a lesser excretion of ammonia and a greater excretion of fixed base was demonstrated in the urine of nephritics In our case 28 there evidently had been severe renal insufficiency and "acidosis" for a considerable time and loss of the fixed base of the body seemed to have included also the calcium of the bones, producing a type of "renal" rickets

The reason for the diminution of serum BCl in the absence of vomiting and edema seems also to lie in the faulty secretion of urine Although our data on this point is not quantitative, it suggests at least that when there is a tendency towards secretion of large quantities of dilute urine, chloride may be present in the urine in considerable amount despite an abnormally low concentration in the serum This is analagous to the chloride loss accompanying the polyuria of some cases of diabetes insipidus and diabetes mellitus It is not inconceivable that such chloride loss in the urine, though relatively little, might eventually deplete the body if the chloride intake were restricted Because of the inability of the kidney to practice base economy, such loss of chloride would also be attended by loss of fixed base

It is of particular interest, however, that the osmotic pressure of the blood neither theoretically nor experimentally was found to be reduced, despite this reduction in $BHCO_3$ and BCl This was due to the fact that non-protein nitrogen was increased to a point sufficient to make up osmotically for the loss of electrolyte from the blood This apparent compensation of a non-electrolyte for electrolyte in the maintenance of normal osmotic pressure in cases of chronic nephritis has also been noted in cases of marked vomiting due to pyloric or intestinal obstruction (2), in which electrolytes have been lost from the body and non-protein nitrogen retained That such a mechanism may exist normally in some of the lower forms of life is suggested by the observation of MacCallum (14) that in the dogfish about one-third

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(1) The concentrations of the principal anions, Cl′, HCO_3', protein, HPO_4'' and lactate, and the actual pH were determined

(2) Total base was determined directly, and from its value and the sum of the five principal acids determined the concentration of undetermined acid was obtained

(3) The principal non-electrolyte substances, non-protein nitrogen (urea) and glucose were determined

(4) The freezing point of the serum was determined and from it the total osmolar concentration of the serum was calculated

(5) A method of calculating the theoretical total osmolar concentration from the concentration of the principal individual solutes, electrolyte and non-electrolyte, was developed

In addition, the composition of the urine was studied to some extent, and after correlation of the observed changes in the chemical composition of the blood serum and urine with the clinical symptoms and findings, it was concluded that

(1) In *acute* hemorrhagic nephritis, marked changes in the chemical composition of the blood occur only when such symptoms as severe vomiting or diarrhea, edema or dehydration, or convulsions occur

(2) When these changes include a reduction of the total electrolyte content of the blood serum, urea is found increased to such an extent that no reduction in osmotic pressure occurs

(3) Such urea increase should be considered compensatory and not due to an inability of the kidney to excrete urea

(4) In *subacute* and *chronic* glomerular nephritis, acute infection causing similar symptoms results in similar changes

(5) In the absence of such symptoms, however, much the same changes occur, but more gradually, as the result of faulty urinary secretion which includes (*a*) failure to practice fixed base economy by substituting ammonia for the fixed base of the plasma salts when the acid radicals are excreted, and (*b*) a failure to secrete urine of normal maximum acidity, i e , free from $BHCO_3$ and (*c*) a failure to retain BCl in the plasma, and (*d*) a failure to excrete sufficiently such acids as phosphoric and sulfuric

(6) The loss of plasma electrolyte due to such faulty urinary secretion is compensated for, osmotically, by retention of urea

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METHOD OF STUDY

Interest in this study was prompted by the clinical observation of what seemed to be an abnormal degree of calcification in the peripheral arteries in older persons with polycythemia vera, as compared to that occurring in normal persons of like age

Fourteen typical cases of polycythemia vera were studied from this viewpoint The spleen was enlarged in all The number of erythrocytes, both absolute and relative, was greatly increased The total blood volume, according to the dye method[2] (11), was greatly increased, owing to the absolute increase in the erythrocytes The patients were hospitalized, three were given the low ionic diet of Keith, Smith and Whelan (11), the others were given the general hospital diet Determinations were made in each case of the calcium content of the whole blood and serum before and following treatment with phenylhydrazine The sodium, potassium, magnesium, phosphate, and the sodium chloride contents of the whole blood and serum were made in five cases before and after treatment with phenylhydrazine

The hemoglobin was determined by the method of Osgood and Haskins For serum sodium the method of Kramer and Tisdall (14), as modified by Whelan, was used For calcium and potassium (13), the methods of Tisdall and Kramer were used Magnesium was determined by the method of Bogert and Plass, which is a combination of Kramer and Tisdall's (15) magnesium method and of Briggs' phosphorus method, sodium sulphite was added to bring out the blue color, as directed by Briggs In the whole blood a modification[3] of the method of Kramer and Tisdall (16) was used for the direct quantitative determination of sodium, potassium, calcium and

[2] The hematocrit determinations were made by the dry oxalate method and a correction of 3 per cent in the cell volume was made for shrinkage

[3] Ten cubic centimeters of blood, accurately measured in a pipette, was laked with about 25 cc of water in a 100 cc. volumetric flask From 10 to 15 cc of 20 per cent trichloracetic acid was added to complete the precipitation of the proteins After the contents had been made up to volume with water, and filtered, 50 cc of the filtrate was evaporated to dryness The method of Kerr was employed in the removal of the trichloracetic acid After the aliquot had been evaporated to dryness again, the residue was dissolved in 0 2 N hydrochloric acid, transferred to a 10 cc volumetric flask and made up to volume

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TABLE 3

Polycythemia vera—studies on the calcium content of the blood and serum before and during treatment with phenylhydrazine

Case	Age	Sex	Date	Hemoglobin	Erythrocytes	Cells by the hematocrit	Blood volume		Plasma volume		Calcium			
											Whole blood		Serum	
							Total	Per kilo	Total	Per kilo	Concentration	Total	Concentration	Total
				grams per cent	*millions*	*per cent*	*cc*	*cc*	*cc*	*cc*	*mgm. per 100 cc*	*mgm*	*mgm per 100 cc*	*mgm*
1	64	M	November 14, 1925	23 0	5 76	60	8,580	136	3,430	54	5 2	445	12 6	432
			December 7, 1925	12 8	2 99	35	4,730	75	3,070	48	7 4	350	13 1	402
2	55	M	December 5, 1926	26 0	7 00	75	14,700	180	3,670	46	3 4	504	14 3	524
			January 4, 1926	12 2	2 82	24	5,650	75	4,290	57	7 5	424	10 1	433
3	50	M	January 11, 1926	25 0	8 18	76	14,250	205	3,420	49	4 0	574	17 3	591
			February 4, 1926	15 2	4 51	38	6,450	104	4,000	64	10 0	645	12 6	504
4	62	M	January 28, 1925	21 4	5 70	65	9,900	173	3,460	60			15 2	526
			February 12, 1925	12 2	4 62	40	6,510	116	3,910	70			9 3	364
5	56	M	April 28, 1925	23 4	7 24	70	11,110	173	3,330	52			15 8	526
			May 6, 1925	20 8	4 97	60	8,760	136	3,500	55			11 9	416
			May 15, 1925	12 5	3 28	37	5,055	81	3,185	51			10 6	336
6	25	M	January 2, 1928	24 5	7 01	60	11,100	203	3,330	61	5 8	679	18 1	602
			January 21, 1928	18 1	5 68	53	7,660	150	3,600	76	5 7	440	11 5	415
7	39	M	January 18, 1928	27 3	7 60	76	17,250	223	4,140	53	3 5	610	12 9	534
			February 13, 1928	24 0	7 56	68	13,750	183	4,400	59	3 8	519	9 8	431
8	66	F	October 4, 1927	27 2	7 23	70	9,725	191	2,925	58	5 0	488	12 9	387
			November 10, 1927	15 3	4 24	47	5,565	114	2,950	60	6 1	340	11 4	336

All determinations were carried out in duplicate on fasting blood, and in several cases the direct method was checked by the trichloracetic acid technic of Kramer and Tisdall (16) Control deter-

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TABLE 4

Polycythemia vera—Studies on the mineral substances of the blood before and during treatment with phenylhydrazine

Case	Age	Sex	Date	Hemoglobin	Erythrocytes	Cells by the hematocrit	Blood volume Total	Blood volume Per kilo	Plasma volume Total	Plasma volume Per kilo	Sodium Serum	Sodium Blood	Potassium Serum	Potassium Blood	Magnesium Serum	Magnesium Blood	Phosphate Serum	Phosphate Blood	Calcium Serum	Calcium Blood	Sodium chloride Serum	Sodium chloride Blood
				gms per cent	millions	per cent	cc	cc	cc	cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc	mgm per 100 cc
1	64	M	November 14, 1925	23 0	5 76	60	8,580	136	3,430	54	325	160	20 1	270	2 2	2 4	2 7	2 1	12 6	5 2	565	305
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			January 4, 1926	12 2	2 82	24	5,650	75	4,290	57	340	114	19 4	135	3 2	5 0	2 5	2 8	10 1	7 5	660	580
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							Total	Per kilo	Total	Per kilo	Serum	Blood	Serum	Blood	Serum	Blood	Serum	Blood	Serum	Blood	Serum	Blood
				gms per cent	*millions*	*per cent*	*cc*	*cc*	*cc*	*cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*
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			May 15, 1925	12 5	3 28	37	5,055	81	3,185	51	358				2 5		2 9		10 6		580	

the assumption that the increased calcium is related to an increase in he serum protein with variation in the colloid-calcium combination In two cases studied, slight increases in the serum proteins were found Studies have not been carried out in our cases to determine whether the diffusible or the nondiffusible fractions, or both, are increased Methods for the study of this question are being developed

The most logical explanation for the hypercalcemia in this disease is that it is related in some manner to the great increase in the absolute number of erythrocytes, since a definite decrease in the calcium levels in the serum follow the reduction in the number of erythrocytes Apparently a relative increase in the ratio of corpuscles to plasma is not accompanied by an increase in the calcium, since normal values were obtained in a case of relative polycythemia vera due to dehydration, in which there were 60 per cent of cells by the hematocrit The absence of an increase in the serum calcium in relative polycythemia vera is in accord with the work of Van Slyke He showed that change does not occur in the inorganic ratios with variations in the relative amount of cells or plasma, since the concentration of the inorganic substances remains the same

It could be assumed that the increased concentration of calcium represents an effort to maintain the normal inorganic ratios in the blood Against this premise is the presence of increased values for serum calcium associated with normal values for serum potassium There is no explanation for the increase in serum potassium in the cases in which it is observed, since it has been shown that this electrolyte does not pass through the cell membrane

The decrease in the percentage concentration of calcium following treatment is due to a decrease in the total calcium of the serum and to dilution from the increased amount of plasma As an example (case 2, table 3), the total serum calcium decreased 17 per cent, the actual plasma volume increased 17 per cent, and the concentration of serum calcium decreased from 17 3 to 12 6 mgm (30 per cent) Approximately half of the percentage change in calcium was related to the variation in the plasma Either the concentration of calcium in the tissue fluid was low or an abnormal excretion of calcium occurred during hemolysis Data regarding the excretion of calcium during the period of blood destruction are lacking

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SUMMARY AND CONCLUSIONS

Fourteen subjects presenting the classic picture of polycythemia vera showed an increase in the serum calcium above the accepted range of normal The values in this substance ranged from 11 1 to 18 1 mgm for each 100 cc of serum The average value was 14 3 mgm

Following treatment with phenylhydrazine and destruction of corpuscles to approximately normal or even subnormal values, the percentage concentration of serum calcium decreased to levels slightly above normal

The basis of the hypercalcemia is not known It may represent a compensatory effort to maintain the inorganic ratios of the blood Hypercalcemia in the human subject can be tolerated without grave disturbance to the organism The susceptibility of patients with polycythemia vera to thrombosis and to high grades of calcification in the peripheral vessels in some cases of polycythemia vera may be late results of hypercalcemia [5]

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1 Bogert, L J, and Plass, E D, Jour Biol Chem, 1923, lvi, 297 The Calcium and Magnesium Content of Fetal and Maternal Blood Serum

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8 Hueper, Wilhelm, Arch Path and Lab Med, 1927, iii, 14 Metastatic Calcifications in the Organs of the Dog after Injections of Parathyroid Extract

[5] We have encountered three cases of mild polycythemia vera during the last three months with volumes of blood, 128, 131 and 140 cc for each kilogram, with serum calcium values of 10 6, 10 4 and 11.3 mgm respectively These data indicate that there are cases of mild degrees of polycythemia vera in which hypercalcemia is probably not present at this stage

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these physiological constants at their normal levels shows that the respiratory function is, in fact, in fair working order. This statement must, however, be qualified, since the other chief function of the respiration—the supply of oxygen to the tissues—is impaired. No actual measurement of the oxygen tension in the tissues has been made, nor of the tension in the arterial blood of pneumonia patients. The oxygen content and capacity of the arterial blood is, however, readily measurable, and from these figures one can obtain an estimate of the efficiency of the respiratory mechanism.

It is probably not inaccurate to say that almost every case of pneumonia shows at some time a deficiency in the oxygen saturation of the arterial blood (2). The fact that there may be oxygen want and still no carbon dioxide retention or shift in the neutrality regulation of the blood is explicable on the basis of the different physical properties of O_2 and CO_2 and the different manner in which they combine with hemoglobin. This subject has been fully discussed by Haldane (3).

Lundsgaard and Van Slyke (4) have attempted to analyze the various factors which contribute to the presence of cyanosis. The origin of cyanosis in pneumonia, it seems safe to state, is respiratory rather than circulatory. It is, however, by no means clear why the blood is incompletely oxygenated in the lungs. Several explanations have been offered for this, viz., unequal expansion of the lungs (5), rapid and shallow breathing (6), diminished lung volume (7), intra-alveolar exudate (8), decreased oxygen diffusion resulting from toxic injury of alveolar walls (9), passage of blood through unaerated channels in the lung (10). It has, moreover, been shown experimentally that an increased rate of blood flow through the lungs may prevent the hemoglobin from taking up its normal load of oxygen (11). Whether this last actually plays a rôle in pneumonia is, to be sure, doubtful, but there seems little doubt that some or all of the other factors may combine to prevent the complete reoxygenation of the blood in its passage through the lungs. Plausible as these explanations may be, the actual proof of their influence and the proper weighting of their importance remains difficult, if not impossible. One can never know the true state of the parenchymatous and vascular lesion in the lung at the time of the arterial oxygen analysis. The relationship of these two must therefore remain a matter of inference and conjecture.

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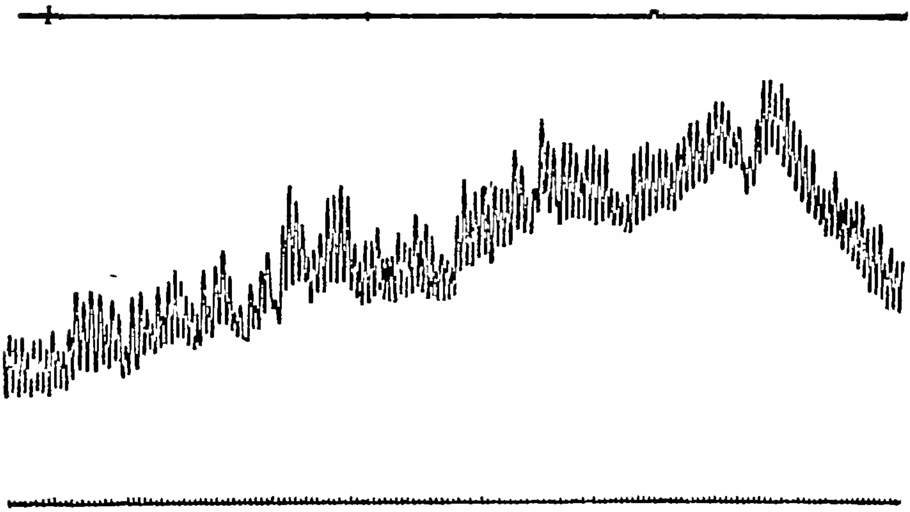
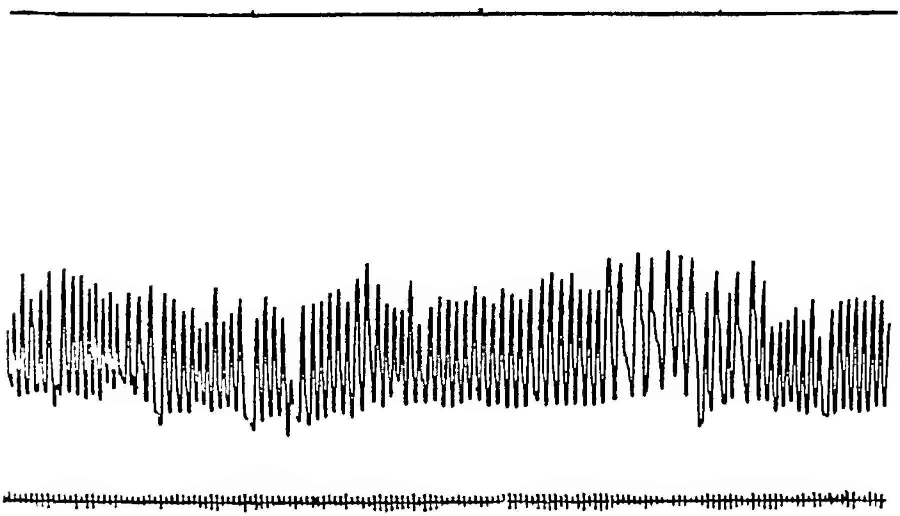


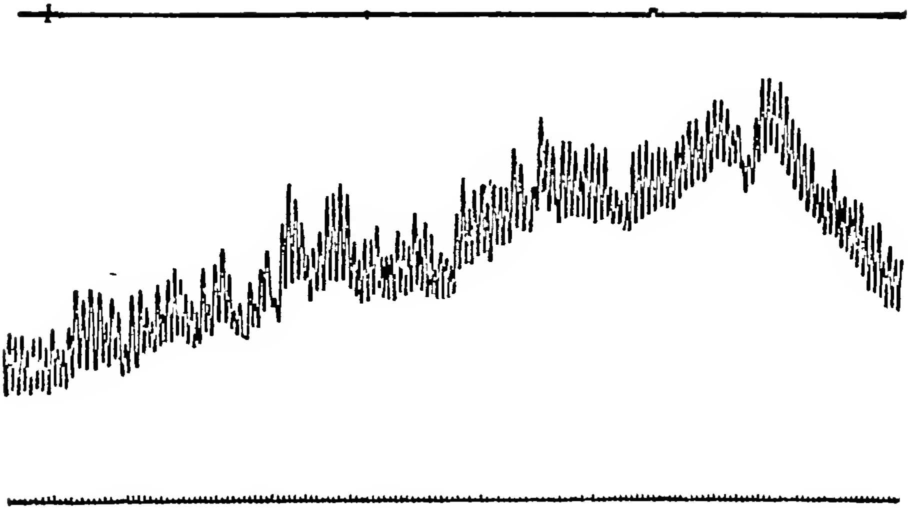
(a)



(b)

Fig 1 (*a*) Plethysmographic Tracing from Case 10, Made on the Fourth Day after Onset of Illness, (*b*) Plethysmographic Tracing from Same Patient Made during Convalescence, on Twenty-Fifth Day after Onset of Illness

The upper line was drawn by the work-adder signal lever Interval between signal lever marks equals 12.34 liters The lower line represents time in 2 second intervals



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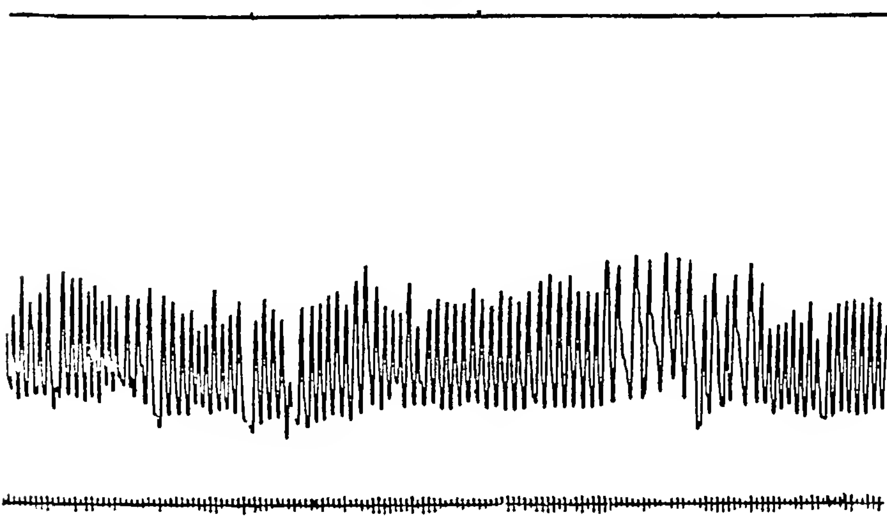

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TABLE 1

Hospital number	Case number	Observation number	Date	Area of pulmonary involvement	Organism	Day after onset	Day of disease temperature was normal	Vital capacity	Minute volume	Tidal air	Respiratory rate	Duration of inspiration	Duration of expiration	Ratio Expiration/Inspiration	Temperature	Pulse rate	O_2 content	O_2 capacity	O_2 saturation	Remarks
								liters	liters	cc		seconds	seconds		°F		volumes per cent	volumes per cent	per cent	
6212	1	1	December 1, 1927	I L I R L I	Group IV Sta aureus	3	30	2 40	10 97	305	36	0 63	0 98	1 55	104 0	120	11 35	16 89	85 0	
		2	December 25, 1927			27		3 98	7 74	537	14 4	1 40	2 22	1 59	100 0	95	15 30	16 23	94 4	Recovered
6232	2	1	December 17, 1927	R M I	Type I	4	9		13 35	417	32	0 81	0 94	1 16	103 5	115	16 83	20 58	81 8	
		2	January 1, 1928	R I I		22		2 73	5 89	420	14	1 19	2 68	2 25	99 0	65	17 86	18 95	94 3	
		3	January 19, 1928			37		2 74	8 04	473	17	1 24	2 18	1 76	98 6		17 85	18 70	95 5	
		4	March 3, 1928			81		3 67	6 17	472	14 2	1 38	2 50	1 81			19 55	20 22	96 7	Recovered
6216	3	1	January 5, 1928	L U L L L L	Type III	4		1 47	15 78	493	32	0 83	0 91	1 09	103 0	116	13 26	16 08	82 5	Died
6217	4	1	January 6, 1928	R U L R M L R L L	Type III	3		1 45	15 42	440	35	0 68	1 02	1 50	104 0	120	14 35	17 79	80 7	Died
6259	5	1	January 11, 1928	R L I	Type I	4	14	1 62	9 38	375	25	0 91	1 31	1 44	101 4	128	17 06	19 24	88 7	
		2	February 10, 1928			31		3 34	7 16	421	17	1 49	2 40	1 61	99 0	84	17 12	18 35	93 4	Recovered
6270	6	1	January 20, 1928	I L I	Type IV	4	4	0 67	6 12	282	21 7	0 95	2 00	2 10	99 8	94	18 50	20 10	92 0	
		2	January 27, 1928			11		1 73	5 62	356	15 8	1 02	2 36	2 31	98 6	70	19 17	20 20	95 3	Recovered

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								liters	*liters*	*cc*		*seconds*	*seconds*		°*F*		*volumes per cent*	*volumes per cent*	*per cent*	
6110	15	1	April 17, 1928	R M L R L L L L L	Group IV	2			12 23	266	46	0 63	0 74	1 17	102 4	144	12 48	18 97	65 8	Died
6111	16	1	April 20, 1928	L L L R U L R L L	Group IV	4			13 18	376	35	0 81	0 78	0 96	102 8	112	18 05	20 60	87 7	Died
6139	17	1	May 29, 1928	L U L L L L R L L R M L	Group IV Tbc.	23		6 57	10 67	331	32 2	0 85	1 04	1 22	102 0	115	13 05	14 18	92 1	Discharged to convalescent home

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6110	15	1	April 17, 1928	R M L R L L L L L	Group IV	2			12.23	266	46	0.63	0.74	1.17	102.4	144	12.48	18.97	65.8	Died
6111	16	1	April 20, 1928	L L L R U L R L L	Group IV	4			13.18	376	35	0.81	0.78	0.96	102.8	112	18.05	20.60	87.7	Died
6139	17	1	May 29, 1928	L U L L L L R L L R M L	Group IV Tbc.	23		6.57	10.67	331	32.2	0.85	1.04	1.22	102.0	115	13.05	14.18	92.1	Discharged to convalescent home

The effect of oxygen inhalation on the respiratory rate and depth

Three patients of the series were studied both while breathing room air and again with the plethysmograph placed inside the oxygen chamber while the patients were permitted to inhale a 40 to 44 per cent oxygen mixture. It was hoped to glean from this procedure further information as to the relative interdependence of rapid and shallow breathing and anoxemia.

Case 14. J. G., male, age 23. Hospital No. 6357. Diagnosis: Lobar pneumonia, empyema, thoracotomy.

Present illness. For 2 days the patient had complained of pain in his left side and chills. He was admitted on March 18, 1928.

Physical examination. Severe pain was obvious. There was slight cyanosis of nail beds and face. The temperature was 105.4°F., pulse 132, respirations 60. The leucocyte count was 34,700. Examination of the chest showed slight dulness over angle of scapula. Below this point breath sounds were suppressed.

X-ray examination. Diffuse opacity from left apex to base, most marked at base.

Bacteriological examination. Group IV pneumococcus and hemolytic streptococcus were recovered from sputum. Blood culture sterile.

Course. Plethysmographic tracings were made before and during oxygen administration. This was accomplished by placing the plethysmograph inside the oxygen chamber. The *first plethysmographic tracing* was made March 19, a day after admission. The temperature was then 103.2°F., pulse 128. The respiratory rate was 44, tidal air 255 cc., and minute volume 11.20 liters. The expiratory-inspiratory ratio was 0.96. The *arterial blood* analysis showed a percentage saturation of 81.7, with the oxygen content and capacity 16.15 and 19.79 vols. per cent, respectively. After these observations had been made the oxygen concentration in the chamber was raised to 44.5 per cent. Two hours later a second series of plethysmographic observations were made. The respiratory rate was now 46.7, tidal air 228 cc., and minute volume 10.67 liters. The ratio of expiration to inspiration was now 1.34. Arterial saturation had increased to 94.4 per cent with an oxygen content of 20.12 vols. per cent and capacity of 21.68 vols. per cent.

Comment on case 14

The result of putting the patient in the chamber was to raise the O_2 content of the arterial blood approximately 4 vols. per cent and to increase the per cent saturation from 81.7 to 94.4. No slowing or deepening of respirations occurred. It may be assumed that the

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gen tension two-fold would, in a measure at least, relieve the condition In this instance we must assume that blood was circulating through unaerated portions of the lungs, and that this rather than rapid and shallow breathing was in the main responsible for oxygen want

Case 16 J M, male, age 32 Hospital No 6414 Diagnosis Lobar pneumonia, septicemia

Present illness The patient had been sick for 3 days, complaining of pain in the left chest, chills, cough, and expectoration of blood tinged sputum He was brought to the hospital on April 19, 1928

Physical examination There was slight cyanosis of nail beds Temperature was 104°F, pulse 120, respirations 36 The leucocyte count was 14,000 The chest signs showed, from spine of left scapula to base posteriorly there was dulness to flatness, voice and breath sounds increased except at very base where they were diminished, bronchial breathing and occasional crepitant râle at angle of left scapula, dulness and occasional sub-crepitant rale at the right base

X-ray examination Opacity of area occupied by left lower lobe, lower part of right upper lobe and right lower lobe

Bacteriological examination Group IV pneumococcus was recovered from the sputum and blood

Course On April 20 the patient was transferred to the oxygen chamber because he was growing more cyanotic and his breathing was becoming more difficult Before oxygen was administered a *plethysmographic record* was made His temperature was then 102 8°F, pulse 112 The respiratory rate was 35, tidal air 376 cc, and minute volume 13 18 liters The *arterial blood* oxygen content was 18 05 vols per cent, with a capacity of 20 60 vols per cent, the saturation being 87 7 per cent

Two and a half hours later, after the patient had been in an atmosphere of 39 5 per cent oxygen for 1½ hours, a *second plethysmographic tracing* was made No significant change had occurred in any of the measurements The respiratory rate was now 35 2, tidal air 372 cc, minute volume 13 08 liters The arterial oxygen content and capacity had risen respectively to 18 54 and 20 80 vols per cent The saturation was now 89 0 per cent In spite of this slight increase the patient's color was obviously better and he said he felt better

The next day the patient became rapidly worse and died on April 23 His blood culture was positive, there being more than 100 colonies to the cubic centimeter of blood

Comment on case 16

The case is similar to the last one, a rapidly fatal pneumonia which did not respond to oxygen therapy either by a significant increase in the per cent saturation of arterial blood or by a slowing or deepening

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The next day the patient became rapidly worse and died on April 23 His blood culture was positive, there being more than 100 colonies to the cubic centimeter of blood

Comment on case 16

The case is similar to the last one, a rapidly fatal pneumonia which did not respond to oxygen therapy either by a significant increase in the per cent saturation of arterial blood or by a slowing or deepening

tion, though it is reasonable to believe that in certain instances it may be an aggravating influence

How much actual acceleration in rate irrespective of diminished depth has to do with inadequate reoxygenation of blood in the lungs has not, heretofore, been considered The shortening of the duration of the inspiratory and expiratory phases and the reduction in the expiratory-inspiratory ratio was, in these patients, the rule during their acute illness The significance of this change is not clear We have the impression, however, that the relative duration of the respiratory phases is of importance from the point of view of pulmonary ventilation

Relatively large values for the minute volume of pulmonary ventilation are found almost without exception during the acute stage of pneumonia, and become smaller during convalescence This has been looked upon by some as of a compensatory nature If so, the compensation is obviously inadequate with respect to the aeration of the blood in the lungs

With regard to the vital capacity, its measurement is perhaps of not much significance except as an indication of pleuritic pain The functional residual air studied by Binger and Brow (7) is of greater interest, and this we believe should be reinvestigated from the point of view of anoxemia

SUMMARY AND CONCLUSIONS

1 By means of a specially designed body plethysmograph the respiratory movements have been studied in a group of patients suffering from acute pneumonia

2 The oxygen content, capacity and per cent saturation have also been measured

3 Observations have been made during the acute stage of the disease during convalescence, after morphine administration and oxygen inhalation

4 Rapid and shallow breathing, and anoxemia are commonly associated phenomena

5 No clear evidence can be adduced, however, that the anoxemia which occurs in lobar pneumonia is the result of rapid and shallow breathing, though in some cases extremely rapid and shallow breath-

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TABLE 1

Data showing effect of morphine on respiratory movements and oxygen saturation of arterial blood of patients suffering from pneumonia

Case number	Hospital number	Date	Dose of morphine	Respiratory rate	Temperature	Pulse	Area of pulmonary involvement	Tidal air	Minute volume	Duration of inspiration	Duration of expiration	Ratio inspiration to expiration	Oxygen content	Oxygen capacity	Per cent saturation	Remarks
			mgm		*F*			*cc*	*liters*	*seconds*	*seconds*		*volumes per cent*	*volumes per cent*		
		1927														
1	6232	December 17	16	32 0*	103 5	115	R M L R I I	417	13 35	0 81	0 94	1 16	16 83	20 58	81 8	Severe pain
				25 0				438	10 96	1 06	1 80	1 70	17 18	20 58	83 6	Recovered
		1928														
2	6216	January 5	18	32 0	103 0	116	I U L I L L	493	15 78	0 83	0 91	1 07	13 26	16 08	82 5	Edema of lung Pleural effusion
				30 5				355	10 83	0 75	1 31	1 75	10 86	16 74	64 9	Treated in oxygen chamber, died
3	6217	January 6	10	35 0	104 0	120	R U I R M L	440	15 42	0 68	1 02	1 50	14 35	17 79	80 7	Respirations very labored
				31 5			R I L	422	14 57	0 75	1 03	1 37				Died
1	6259	January 11	12	25 0	101 4	128	R L I	375	9 38	0 91	1 31	1 44	17 06	19 24	88 7	Pain Serum treatment
				22 0				357	7 86	0 99	1 82	1 84	17 40	20 00	87 0	Recovered
5	6262	January 17	10	21 0	100 0	80	R L L	405	8 50	1 41	1 71	1 21	16 69	18 41	90 7	Not acutely ill
				19 6				348	6 83	1 50	2 12	1 41	17 06	18 42	92 6	Recovered
6	6261	January 16	12	40 0	103 0	108	R U L R L L						17 09	20 08	85 2	Died
				42 0	103 8	120							16 86	20 05	84 1	

TABLE 1

Data showing effect of morphine on respiratory movements and oxygen saturation of arterial blood of patients suffering from pneumonia

Case number	History number	Date	Dose of morphine	Respiratory rate	Temperature	Pulse	Area of pulmonary involvement	Tidal air	Minute volume	Duration of inspiration	Duration of expiration	Ratio inspiration to expiration	Oxygen content	Oxygen capacity	Per cent saturation	Remarks
			mgm		*F*			*cc*	*liters*	*seconds*	*seconds*		*volumes per cent*	*volumes per cent*		
		1927														
1	6232	December 17	16	32.0*	103.5	115	R M L R L L	417	13.35	0.81	0.94	1.16	16.83	20.58	81.8	Severe pain
				25.0				438	10.96	1.06	1.80	1.70	17.18	20.58	83.6	Recovered
		1928														
2	6216	January 5	18	32.0	103.0	116	L U L L L L	493	15.78	0.83	0.91	1.07	13.26	16.08	82.5	Edema of lung Pleural effusion
				30.5				355	10.83	0.75	1.31	1.75	10.86	16.74	64.9	Treated in oxygen chamber, died
3	6217	January 6	10	35.0	104.0	120	R U L R M L	440	15.42	0.68	1.02	1.50	14.35	17.79	80.7	Respirations very labored
				31.5			R L L	422	14.57	0.75	1.03	1.37				Died
4	6259	January 11	12	25.0	101.4	128	R L L	375	9.38	0.91	1.31	1.44	17.06	19.24	88.7	Pain. Serum treatment
				22.0				357	7.86	0.99	1.82	1.84	17.40	20.00	87.0	Recovered
5	6262	January 17	10	21.0	100.0	80	R L L	405	8.50	1.41	1.71	1.21	16.69	18.41	90.7	Not acutely ill
				19.6				348	6.83	1.50	2.12	1.41	17.06	18.42	92.6	Recovered
6	6261	January 16	12	40.0	103.0	108	R U L R L L						17.09	20.08	85.2	Died
				42.0	103.8	120							16.86	20.05	84.1	

TABLE 1—*Continued*

Case number	Hospital number	Date	Dose of morphine	Respiratory rate	Temperature	Pulse	Area of pulmonary involvement	Tidal air	Minute volume	Duration of inspiration	Duration of expiration	Ratio inspiration to expiration	Oxygen content	Oxygen capacity	Per cent saturation	Remarks
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15	6317	March 13	16†	12 5	103 5	100	L U L L L L	278	11 83	0 66	0 69	1 05	15 34	17 23	89 0	Severe pain
				31 1				284	9 70	0 81	0 92	1 13	15 10	16 68	90 6	Recovered
16	6352	March 11	12	72 0	102 8	128	L U L L L L	127	9 14	0 52	0 58	1 11	15 30	19 26	79 4	Pain
				64 0			R M L	174	11 03	0 44	0 44	1 00	15 05	19 94	75 5	Recovered
17	6358	March 20	16	44 0	104 6	96	R U L						13 75	17 87	76 9	Râles throughout both lungs
		March 20		36 0	104 1	106							13 96	18 91	73 5	Recovered
18	6439	May 29	18	32 2	100 1	108	L U L L L L	331	10 67	0 85	1 04	1 22	13 05	14 18	92 1	Moist râles throughout
				25 1			R U L R M L	262	6 38	0 87	1 77	2 04	11 47	14 20	80 8	In sanitarium
19	6464	June 9	18	24 2	99 8	82	L L L	304	7 37	1 10	1 30	1 18	16 46	19 05	86 4	Bronchopneumonia
				22 1				236	5 21	1 04	1 62	1 56	16 17	18 90	85 5	Recovered

* The first observation of each pair was made before morphine was given, the second 15 to 30 minutes after

† 240 mgm caffeine

‡ Plus 192 mgm caffeine.

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Case number	Hospital number	Date	Dose of morphine	Respiratory rate	Temperature	Pulse	Area of pulmonary involvement	Tidal air	Minute volume	Duration of inspiration	Duration of expiration	Ratio inspiration to expiration	Oxygen content	Oxygen capacity	Per cent saturation	Remarks
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		March 20		36 0	104 1	106							13 96	18 91	73 5	Recovered
18	6439	May 29	18	32 2	100 1	108	L U L L L L	331	10 67	0 85	1 04	1 22	13 05	14 18	92 1	Moist râles throughout
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morphine on the respiratory movements, and (II) the effect of morphine on the oxygen saturation of the arterial blood. The relationship of these two has been considered elsewhere (9). The data are tabulated in table 1.

I. The respiratory movements of 15 patients were studied in the plethysmograph before and after morphine administration.

1. Rate. In all but one case there was a drop in rate. The average drop in 14 cases was 4.4 to the minute. The greatest fall was from 42.5 to 31.1. In one patient (number 6289) the rate increased from 40 to 42 per minute. His tidal air, however, fell from 244 to 186 cc., and his minute volume from 9.78 to 7.81 liters. His breathing indicated edema of the lungs, and at the time of observation he was rapidly growing worse. His arterial saturation dropped from 85.9 to 84.7 per cent after morphine, a change of little, if any, significance.

2. Tidal air. In 10 cases there was a drop in tidal air, the greatest drop being 138 cc. This occurred in patient number 6216, whose arterial saturation diminished 21.5 per cent. The average drop in tidal air was 57.7 cc. In the remaining 5 cases the tidal air increased, the greatest increase being 102 cc. In these 5 cases, pleuritic pain was a prominent symptom, and relief of pain by morphine probably allowed deeper breathing with more comfort. In one of the 5 cases 192 mgm. of caffeine were given with the morphine. These will be considered later. In no one of these 5 cases was the increase in arterial saturation as great as 1 per cent.

3. Minute volume. In 13 cases the minute volume was diminished after morphine. The greatest drop in minute volume was 4.95 liters and the smallest was 0.85 liter, the average being 2.20 liters.

Two patients (numbers 6295 and 6352) showed an increase in minute volume. In both of these the breathing was extremely shallow and the rate correspondingly rapid. In the one case the rate was 42.3 and the tidal air was 196 cc., while in the other the rate was 72 and the tidal air was 127 cc. In the first patient the minute volume increased from 8.22 to 10.51 liters, and in the second it increased from 9.14 to 11.03 liters. Both patients were very ill. The first had two lobes involved, and the second had three. In neither were there any signs of edema of the lungs. In the second patient there seems to have been a psychic element in the excessively rapid respirations,

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I. The respiratory movements of 15 patients were studied in the plethysmograph before and after morphine administration.

1. *Rate.* In all but one case there was a drop in rate. The average drop in 14 cases was 4.1 to the minute. The greatest fall was from 42.5 to 31.1. In one patient (number 6289) the rate increased from 40 to 42 per minute. His tidal air, however, fell from 244 to 186 cc., and his minute volume from 9.78 to 7.81 liter. His breathing indicated edema of the lung, and at the time of observation he was rapidly growing worse. His arterial saturation dropped from 85.9 to 84.7 per cent after morphine, a change of little, if any, significance.

2. *Tidal air.* In 10 cases there was a drop in tidal air, the greatest drop being 138 cc. This occurred in patient number 6246, whose arterial saturation diminished 21.5 per cent. The average drop in tidal air was 57.7 cc. In the remaining 5 cases the tidal air increased, the greatest increase being 102 cc. In these 5 cases, pleuritic pain was a prominent symptom, and relief of pain by morphine probably allowed deeper breathing with more comfort. In one of the 5 cases 192 mgm. of caffeine were given with the morphine. These will be considered later. In no one of these 5 cases was the increase in arterial saturation as great as 1 per cent.

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TABLE 2

Data showing the average effect of several doses of morphine on the respirations of patients suffering from pneumonia

History number	Total dose of morphine	Number of doses given	Area of pulmonary involvement	Average rate before morphine	Average rate ½ to 1½ hours after morphine	Change in rate	Rate before last dose	Rate after last dose	Change in rate	Number of hours during which morphine was given	Remarks
Group A											
	mgm										
6259	28	2	R L L	28 5	27 0	−1 5	25 0	22 0	−3 0	8	Dry râles
6272	28	3	L L L L U L	42 7	40 7	−2 0	38 0	38 0	0	17	Dry râles, friction rub
6316	56	5	R. L L	25 5	24 0	−1 5	24 0	24 0	0	120	Dry râles, friction rub
6317	38	3	L L L	30 5	29 0	−1 5	34 0	30 0	−4 0	30	Dry râles
6335	40	3	R. U L	28 7	26 6	−2 1	24 0	22 8	−1 2	22	Dry râles
6347	36	4	L U L L L L	36 2	30 5	−5 7	36 0	32 0	−4 0	70	Dry râles
6352	22	2	L U L L L L R. M L	59 0	55 0	−4 0	46 0	46 0	0	11	Dry râles, friction rub
6368	30	3	R. M L R. L L	38 0	36 0	−2 0	40 0	38 0	−2 0	43	Dry râles, few moist râles at bases, pleural effusion, mitral stenosis

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Group A											
	mgm										
6259	28	2	R L L	28.5	27.0	−1.5	25.0	22.0	−3.0	8	Dry râles
6272	28	3	L L L L U L	42.7	40.7	−2.0	38.0	38.0	0	17	Dry râles, friction rub
6316	56	5	R. L L	25.5	24.0	−1.5	24.0	24.0	0	120	Dry râles, friction rub
6317	38	3	L L L	30.5	29.0	−1.5	34.0	30.0	−4.0	30	Dry râles
6335	40	3	R. U L	28.7	26.6	−2.1	24.0	22.8	−1.2	22	Dry râles
6347	36	4	L U L L L L	36.2	30.5	−5.7	36.0	32.0	−4.0	70	Dry râles
6352	22	2	L U L L L L R. M L	59.0	55.0	−4.0	46.0	46.0	0	11	Dry râles, friction rub
6368	30	3	R. M L R. L L	38.0	36.0	−2.0	40.0	38.0	−2.0	43	Dry râles, few moist râles at bases, pleural effusion, mitral stenosis

TABLE 2—*Continued*

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Group B—Continued											
	mgm										
6439	54	4	R U L R. M L R. L L L U L L L L	41 5	35 8	−5 7	32 2	25 1	−7 1	432	Extensive involvement, many moist râles, tuberculosis
6451	62	6	R U L R M L R L L	38 0	30 8	−7 2	40 0	38 0	−2 0	158	Moist râles. Treated in oxygen chamber
Group C											
6264	78	7	R. U L R L L	44 4	45 2	+0 8	42 0	48 0	+6 0	108	Moist and musical râles throughout both lungs, very jaundiced Treated in oxygen chamber
6289	36	3	R U L R L L	45 3	43 3	−2 0	48 0	48 0	0	10	Moist râles throughout. Treated in oxygen chamber
6291	94	10	R. U L R. L L	39 4	37 4	−2 0	60 0	48 0	−12 0	192	Friction rub, pleural effusion, moist râles. Treated in oxygen chamber

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cluded in the table We believe that this delayed slowing of the rate is in part at least due to the cumulative action of morphine

We have also studied the effect of caffeine on the respiratory movements and arterial saturation of one patient (number 7347) He was observed on 2 successive days while acutely ill On the first day he was given 240 mgm of caffeine sodium benzoate, and on the second day he was given 192 mgm of caffeine and 12 mgm of morphine After caffeine alone, his rate, tidal air, minute volume, and per cent saturation increased, while the morphine and caffeine together resulted in a reduction in rate, but a slight increase in tidal air and per cent saturation The minute volume on this occasion was smaller after the drug was given than before None of these changes was of sufficient magnitude to attach much importance to them, but at least they are different from those observed after morphine alone That codeine in moderate amounts may have a detrimental effect on the respiratory center is suggested by case number 6213, whose respiratory rate dropped to 14 and whose arterial saturation dropped to 40 per cent after he had had 24 mgm of morphine in addition to 236 mgm of codeine, which he had received during a period of 3½ days His breathing was of the Cheyne-Stokes type, his lungs were filling with exudate, he rapidly passed into coma, and, had he not been immediately put into the oxygen chamber, he would in all probability have died The next morning, while breathing a 40 per cent oxgen mixture, his arterial saturation was 90 3 per cent and his respiratory rate was 18

II Effect of morphine on the oxygen saturation of the arterial blood In 16 patients out of 20 on whom oxygen analyses of the arterial blood were done before and after morphine, there was a drop in the arterial saturation The greatest drop was 21 3 per cent and the average drop was 5 per cent (table 1) Of the remaining 4 cases, 3 showed a slight rise in O_2 saturation after morphine In one no analysis was made One of these 3 cases (number 6232) had severe pain, which was relieved by morphine His tidal air increased from 412 to 438 cc , though his minute volume dropped from 13 35 to 10 96 liters Another, case number 6262, was not acutely ill, and the third (case number 6347) was given caffeine with the morphine Moreover, in his case pain was relieved by morphine and his tidal air increased

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DISCUSSION

In most cases of pneumonia the effect of morphine on the respiratory movements and on the arterial oxygen saturation is slight Certainly the depression of respiration which follows morphine administration is ordinarily not sufficient to contraindicate its use The benefits which may accrue to the patient in the direction of relief from pain, reduction of metabolism, and sleep, undoubtedly outweigh the possible ill effects of a slight reduction in pulmonary ventilation and increase of anoxemia

Occasionally, however, morphine may so diminish pulmonary ventilation as to result in serious oxygen want This is liable to occur in patients in whom the pulmonary involvement is extensive and is accompanied by diffuse moisture, and in patients who are already suffering from severe oxygen want Because of the possibility of this type of reaction to it, morphine must always be used with caution and is best combined with oxygen therapy

lungs breath sounds were bronchovesicular and numerous rhonchi were heard She appeared cyanotic Blood culture was positive for Type II pneumococcus She was transferred to the oxygen chamber on the day the morphine test was made The next day her arterial saturation was 93 2 per cent Five days later she died (3) In patient number 6439 the saturation fell from 92 1 to 80 8 per cent He had been acutely ill for 12 days Tubercle bacilli had been demonstarted in his sputum His temperature fluctuated from 101° to 104°F The only uninvolved part of his lungs was the lower right lobe, which was clear when the arterial punctures were done Moist râles were present throughout both lungs Figure 1, *a* and *b*, shows parts of his respiratory tracing before and after morphine administration These 3 patients in whom morphine administration resulted in a definite and perhaps serious unsaturation of the arterial blood were all extremely ill Moreover, they showed not only extensive lung involvement, but the presence of diffuse, moist râles It is to be noted that in none was anoxemia severe before morphine A fourth case already referred to is not included here, since no arterial blood analysis was made before morphine After morphine injection, however, his saturation was only 40 per cent

DISCUSSION

In most cases of pneumonia the effect of morphine on the respiratory movements and on the arterial oxygen saturation is slight Certainly the depression of respiration which follows morphine administration is ordinarily not sufficient to contraindicate its use The benefits which may accrue to the patient in the direction of relief from pain, reduction of metabolism, and sleep, undoubtedly outweigh the possible ill effects of a slight reduction in pulmonary ventilation and increase of anoxemia

Occasionally, however, morphine may so diminish pulmonary ventilation as to result in serious oxygen want This is liable to occur in patients in whom the pulmonary involvement is extensive and is accompanied by diffuse moisture, and in patients who are already suffering from severe oxygen want Because of the possibility of this type of reaction to it, morphine must always be used with caution and is best combined with oxygen therapy

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In spite of the wide use of oxygen in pneumonia, comparatively few figures have been published concerning the degree of arterial oxygen unsaturation which occurs in the disease or the changes in saturation which follow oxygen therapy Our study presents the results of over 300 arterial punctures and oxygen analyses made in 137 patients The paper is divided into two parts, the first dealing with frequency tables having to do with the distribution of arterial oxygen saturations and a consideration of them in relation to the type of invading organism, survival of patients, and the effect of oxygen inhalation The second part of the paper deals with a description of a few individual cases selected because of their extreme anoxemia and because in several of them autopsies were performed and long findings observed not long after the oxygen analyses of the arterial blood were performed

MATERIAL AND METHODS

The patients studied were all admitted to the Hospital of The Rockefeller Institute with the diagnosis of acute pneumonia The great majority were pneumonias of the lobar type, though in a few the distribution of the signs and the clinical history were that of bronchopneumonia No selection was made in this series with the exception that in general arterial bleedings were performed on the more seriously ill and on those with the more intense cyanosis

The blood was usually obtained from the femoral artery with the technique suggested by Fraser (9) No harm or inconvenience was ever found to come from this procedure in approximately 300 punctures One patient was bled nine times in 12 days without ill effect The blood was transferred from the syringe to small tonometers, where it was oxalated and kept over mercury In most instances duplicate analyses of oxygen content and capacity were

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Stadie (8) observed in a series of 33 pneumonia cases that there was only one case which recovered in which the arterial unsaturation of the blood was greater than 20 per cent It would be of interest to know whether in a larger series the degree of anoxemia and mortality showed as close a correlation even though they may not be caus-

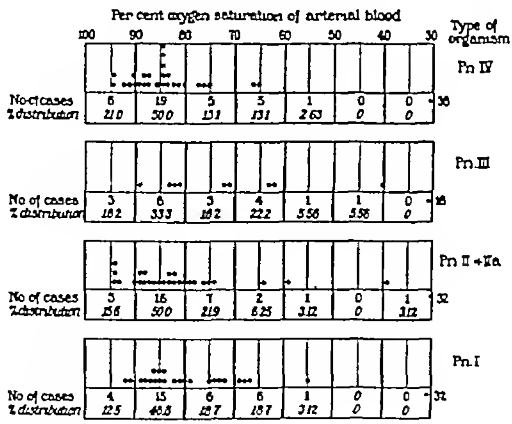

FIG 2 FREQUENCY TABLE SHOWING DISTRIBUTION OF PER CENT OXYGEN SATURATION OF ARTERIAL BLOOD ARRANGED ACCORDING TO THE TYPE OF INFECTING ORGANISM

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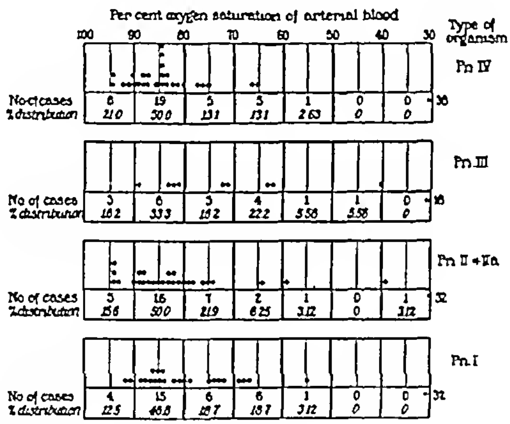

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reached this level (fig 5) The reasons why the more gravely ill patients fail to reach a normal arterial oxygen saturation when exposed to 40 per cent oxygen will be discussed in the consideration of individual patients in the second part of this paper

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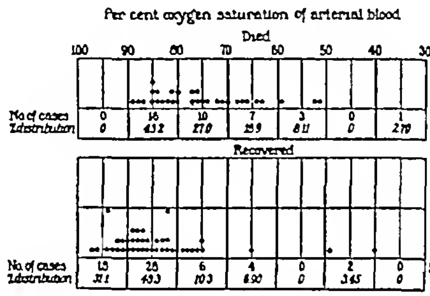

FIG 4 FREQUENCY TABLE SHOWING COMPARISON OF DISTRIBUTION OF ARTERIAL OXYGEN SATURATION IN FATAL AND RECOVERED CASES NOT TREATED BY TYPE I ANTIPNEUMOCOCCUS SERUM

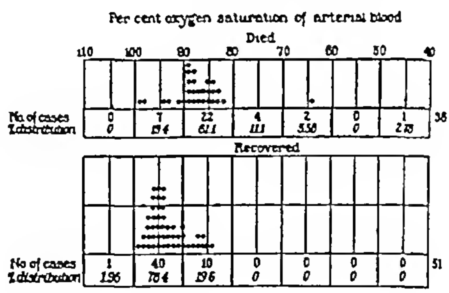

FIG 5 FREQUENCY TABLE SHOWING DISTRIBUTION OF ARTERIAL OXYGEN SATURATION IN PATIENTS AFTER EXPOSURE TO 40± PER CENT OXYGEN COMPARISON OF FATAL AND RECOVERED CASES

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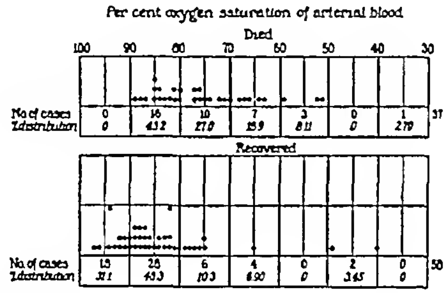

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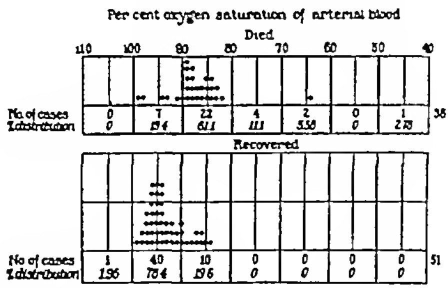

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PART II

Eight of 130 cases tabulated in figure 1 showed an oxygen saturation below 60 per cent A more detailed consideration of these cases will be profitable both from the point of view of inquiring into the causes of anoxemia and of explaining why certain patients, when placed in the chamber, exhibit no increase in the per cent oxygen saturation of their arterial blood

Case 1 (Hospital No 5811) Lobar pneumonia, septicemia (Pneumococcus Type II) Died

The patient was a male, aged 37, who entered the hospital after 2 days of acute illness On admission there was slight cyanosis and evidence of pneumonic consolidation of the upper two-thirds of the right lung Three days later the patient's condition became definitely worse Cyanosis was intense and diffuse and the patient could be aroused only with difficulty The signs in the right chest had extended to the base, where many medium and coarse râles could be heard

The arterial blood was only 39 4 per cent saturated with oxygen, the content and capacity being 5 94 and 15 06 vols per cent respectively At this time the patient was breathing 30 to the minute He was transferred to the oxygen chamber and kept in an atmosphere containing 42 per cent oxygen until he died, approximately 16 hours later One and one-half hours after admission to the chamber the arterial O_2 content was 14 vols per cent, the capacity 16 7 vols per cent and the per cent saturation 83 8 The respiratory rate at this time was 36 Twelve hours before death blood culture showed 29 colonies of Type II pneumococcus per cubic centimeter of blood No permission for autopsy was granted

Comment

The significant feature of this case is the intense anoxemia coming on simultaneously with a spread to the right lower lobe The fact that in this region there was only moderate dulness but many medium and coarse râles appears to be of importance It is this type of freshly spread early lesion in the presence of a heavy blood invasion which is so frequently associated with intense arterial anoxemia

Case 2 (Hospital No 5418) Lobar pneumonia (Pneumococcus Type II) Died

The patient, a male, aged 56, entered the hospital on the second day of illness There was evidence of pneumonic consolidation in the right lower lobe, with coarse râles and a friction rub to be heard in the left scapular region The patient's condition gradually became worse Four days later both lungs were full

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Case 4 (Hospital No 5413) Male, aged 52 Lobar pneumonia (Pneumococcus Type III) Died

The patient came to the hospital on the third day of illness There was marked diffuse cyanosis The arterial blood was 52 1 per cent saturated Signs of consolidation were confined to the lower right back, where there were numerous moist râles Musical râles were scattered throughout the chest on both sides and expiration was prolonged

The patient was transferred to the oxygen chamber, which was charged to 41 5 per cent O_2 Twelve hours later dyspnea and cyanosis were unimproved Breathing was asthmatic Breath sounds were suppressed over the lower half of the right chest in back, where there were dulness and fine râles There was much mucus in the upper respiratory tract The O_2 content was now 12 45 and capacity 13 75 vols per cent The per cent saturation was therefore 90 6 The next 12 hours brought a distinct change for the worse The patient's face was purple and he was gasping for breath Loud tracheal râles were present Examination of the chest was not satisfactory because of patient's condition Blood culture showed 10 colonies of Pneumococcus Type III per cubic centimeter of blood The arterial blood had dropped to a saturation of 62 5 per cent, the content and capacity being 4 40 and 7 05 respectively

At autopsy the left lung was found to be quite normal and weighed 550 grams The right lung, however, weighed over 2 kilograms On section all three lobes appeared to be equally consolidated The cut surface was firm, granular, dark reddish and quite moist Frothy, bloody fluid exuded from the smaller bronchi

Comment

The first response to oxygen was a satisfactory one as far as the saturation of the arterial blood was concerned With increasing amount of moisture in the air spaces of the right lung aeration of the blood was impeded and marked anoxemia occurred in spite of oxygen inhalation The autopsy findings provided a satisfactory explanation for this, there being an involvement of the entire right lung which contained no air and much fluid

Case 5 (Hospital No 5490) Female, aged 48 Lobar pneumonia (Pneumococcus Type I) Recovered

Four days before admission the patient had a sudden shaking chill On admission she appeared to be very ill There was intense cyanosis of the finger tips Signs of consolidation were present in the left lower lobe Blood culture showed 3 colonies of Pneumococcus Type I per cubic centimeter The following day the patient's condition was somewhat worse Blood culture was still positive She was very cyanotic Temperature was 103 4°F , pulse 130, respirations 38 The arterial saturation was 55 2 per cent, O_2 content 6 76 and O_2 capacity 12 26 vols

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Comment

This case is typical of the influenzal bronchopneumonias in which extreme oxygen want is a prominent feature with pulmonary signs characterized by widespread coarse râles rather than evidence of localized consolidation It is these patients for whom oxygen therapy is especially useful The drop in temperature following admission to the chamber is, in the light of Boothby's observations (5), perhaps more than a coincidence

Case 7 (Hospital No 6213) Male, aged 49 Lobar pneumonia (Pneumococcus Type III) Recovered

The patient was taken sick 3 days before he entered the hospital On admission on December 1, 1927, he showed only slight cyanosis of the lips and nail beds At this time the lung signs consisted of suppression of breath sounds and friction rub in the right axilla, with dulness and almost completely suppressed breath sounds in the right back, below the angle of the scapula Two days later cyanosis was slightly increased and the physical signs suggested a spread to the upper lobe of the right lung Numerous dry râles were now present X-ray showed opacity throughout the right upper lobe and parts of middle and lower lobes The next day the patient was obviously worse There had been a still further spread in the right axilla Cough was very troublesome, and it was necessary to give codeine At 9 15 p m he was given 12 mgm of morphine Not long after the patient's respiratory rate dropped to 10, cyanosis became intense, and he developed Cheyne-Stokes breathing His lungs were filling with fluid and he rapidly passed into coma An arterial puncture showed the blood to be only 40 2 per cent saturated with oxygen, the content being 6 86 vols per cent and the capacity 17 08

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A statistical estimate of the therapeutic value of oxygen in pneumonia would at present have little value The number of cases is far too small for such an analysis and the character of the material too complex We have had to content ourselves with the construction of simple frequency tables to study the per cent distribution of the various grades of anoxemia There appears to be a positive correlation between anoxemia and mortality Moreover, the level of oxygen saturation in the arterial blood of a patient exposed to 40 per cent oxygen is of prognostic importance, since the survivors usually reach a level above 90 per cent, while the fatal cases do so far less often

We have made no effort to give complete clinical reports on all our cases because the space available will not permit this Furthermore, an analysis of this sort is extremely confusing The patient's condition alters so quickly in pneumonia that one can seldom be sure whether the changes observed after exposure to oxygen are determined by this or are part of the normal variations of the disease In general we may state that, aside from conspicuous improvement in color, the other changes usually encountered were slight diminution in pulse and respiratory rate and improvement in the patient's mental state These observations are in agreement with those observed by the authors already referred to Boothby's recent finding (5) of a reduction of fever following oxygen administration is of much interest That this has not been striking on our cases may perhaps be accounted for by the fact that they were mostly lobar pneumonias seen as a rule on the third to fifth day of disease and not post-operative bronchopneumonias placed in a chamber shortly after the diagnosis was made

In a small group of cases selected because of severe anoxemia (oxygen saturation below 60 per cent) we have considered the physical signs and autopsy findings in relation to the arterial oxygen saturation The presence of extensive, rapidly spreading pulmonary lesions with much moisture, exudate or transudate, appears to be common to this group In what manner this type of lesion brings about anoxemia we are not yet certain It is in part due to diminished lung volume, in part due to passage of blood through unaerated channels Such a

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The author expresses his gratitude to his former associates, Drs G R Brow, Douglas Boyd, R L Moore, J M Faulkner, R V Christie and J S Davis, Jr, for their cooperation and assistance in this work

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The author expresses his gratitude to his former associates, Drs G R Brow, Douglas Boyd, R L Moore, J M Faulkner, R V Christie and J S Davis, Jr, for their cooperation and assistance in this work

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Inability to correlate satisfactorily the experimental observation Birkhaug with the well established clinical phenomena of erysip has led to the present study Three aspects of the subject have b investigated (1) the reactivity of the skin of erysipelas patient intracutaneous injections of filtrates of erysipelas streptococci, (2) presence of a toxic substance in the blood of patients acutely ill v erysipelas, and (3) the capacity of the serum of erysipelas patient neutralize the toxic action of culture filtrates

SKIN REACTIVITY OF PATIENTS WITH ERYSIPELAS TO FILTRATES ERYSIPELAS STREPTOCOCCI

The skin reactions to sterile filtrates from broth cultures of erysi las streptococci were studied in 30 patients with erysipelas at interv during the acute and convalescent stages of the disease With exception the patients were all on the adult medical wards of the N Haven Hospital, their ages ranging from 13 to 70 years The filtra employed in most instances were prepared in our laboratory fr cultures of hemolytic streptococci cultivated directly from the lesi of typical cases of erysipelas For comparison a standardiz erysipelas toxin obtained from the Squibb Laboratories through t courtesy of Dr J F Anderson was used in some of the cases

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The results as charted demonstrate that 20 cases (Group I) showed on the first test during the active stage of the disease either no reaction or only a very slight degree of reactivity of somewhat doubtful

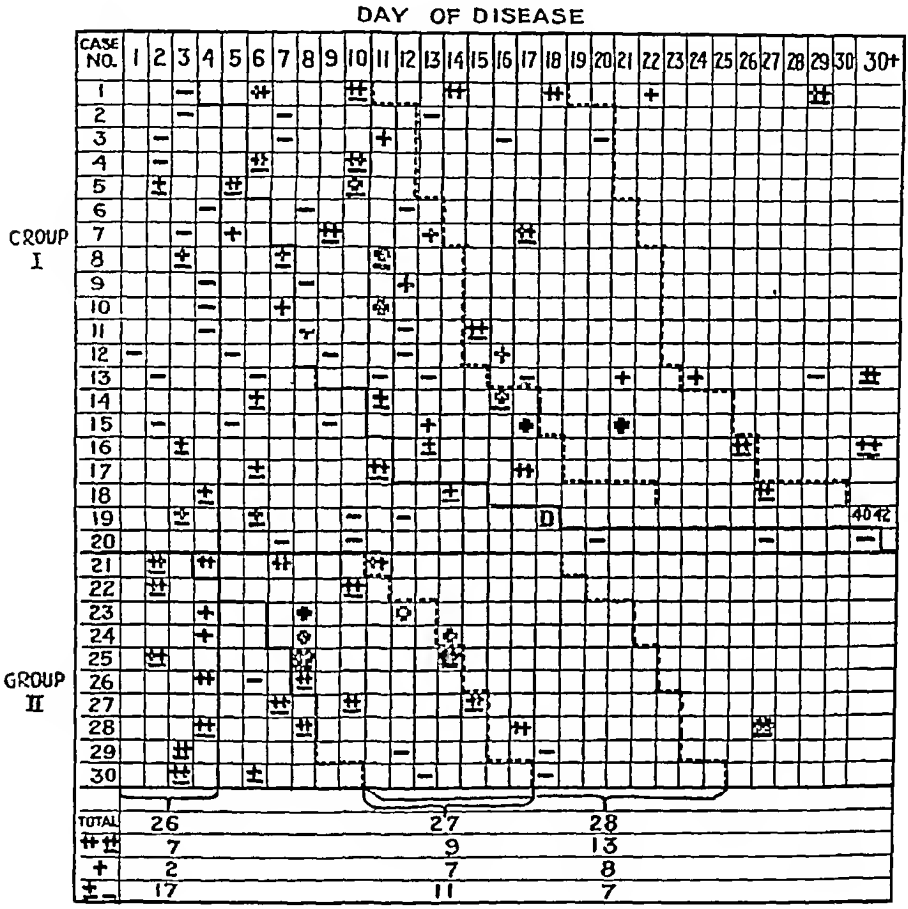

CHART 1 SKIN REACTIVITY OF ERYSIPELAS PATIENTS

— = non-reactive, ± = reactive to 30 or 50 S T D , + = reactive to 10 S T D , ±± = reactive to 3 or 5 S T D , ++ = reactive to 1 S T D The broken staggered lines mark the end of 7 and 15 day periods, respectively, after return of temperature to normal

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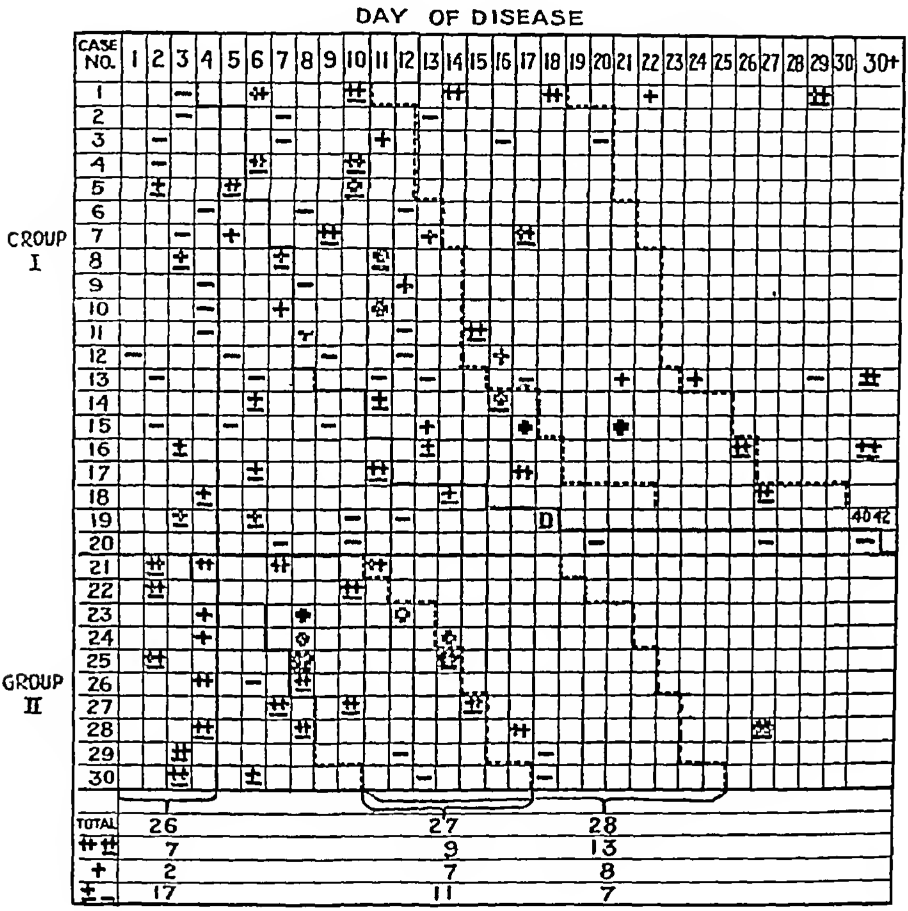

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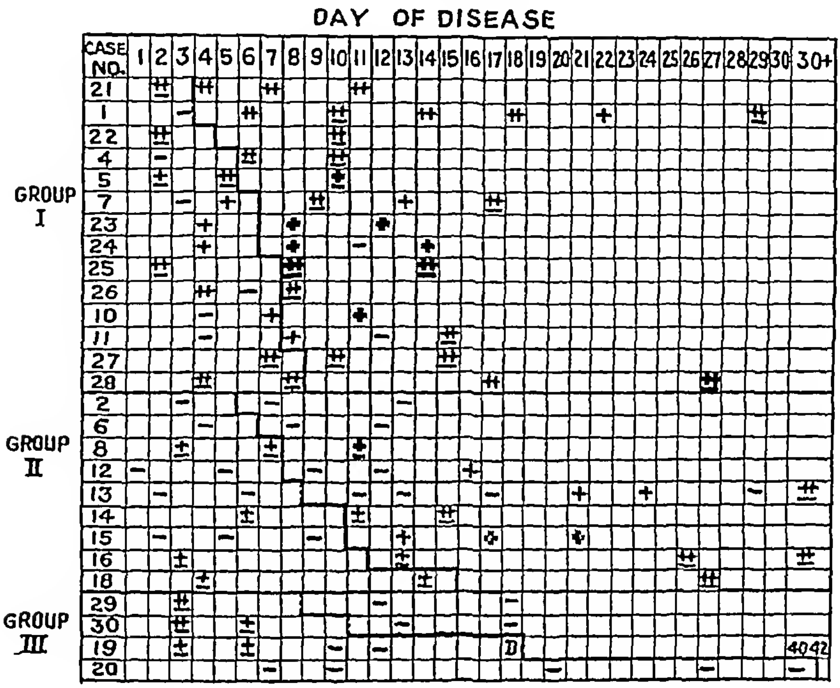

Chart 2 Relationship of Skin Reactivity to Clinical Course of Erysipelas

Case 1 Readmission of Case 13 Recurrence on 8th day of 24 hour's duration Case 13 Recurrences on the 20th and 29th days both of which lasted approximately 48 hours Case 29 Abscess developed about left eye on 8th day and was incised on the 12th day Case 30 On the 16th day patient had recurrence over entire area previously involved and at that time a blood culture yielded hemolytic streptococci The recurrence lasted 36 hours Case 19 Abscesses developed on arms beginning on the 7th day Hemolytic streptococcus septicemia developed on the 13th day Exitus on the 18th day Case 20 Migrating erysipelas with metritis, arthritis and septicemia complicating pregnancy and the puerperium Recovery on 42nd day

In chart 2 the cases have been rearranged into three groups in order to bring out more clearly the relationship between the skin tests and the course of the disease In Group I are the 14 cases which showed

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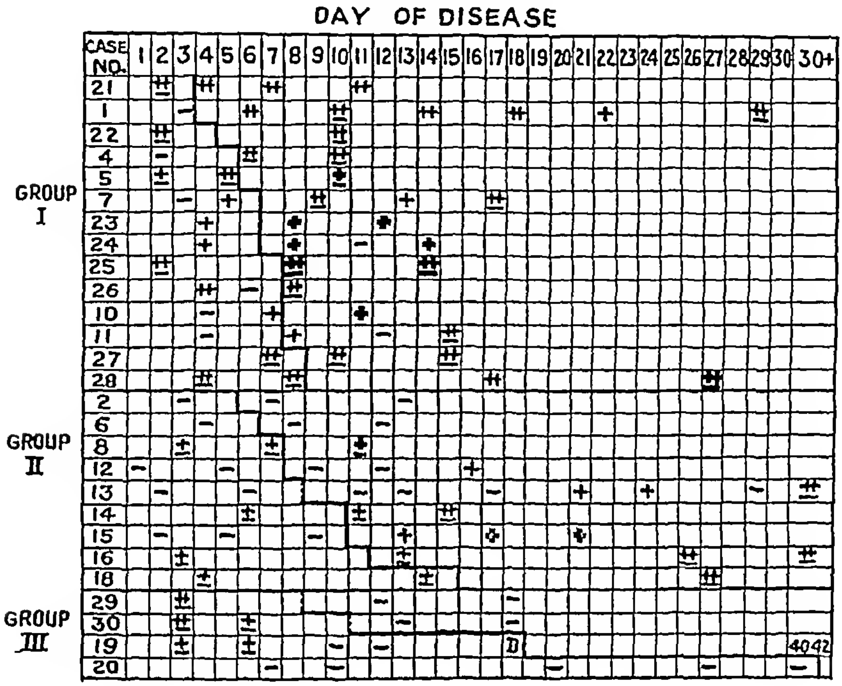

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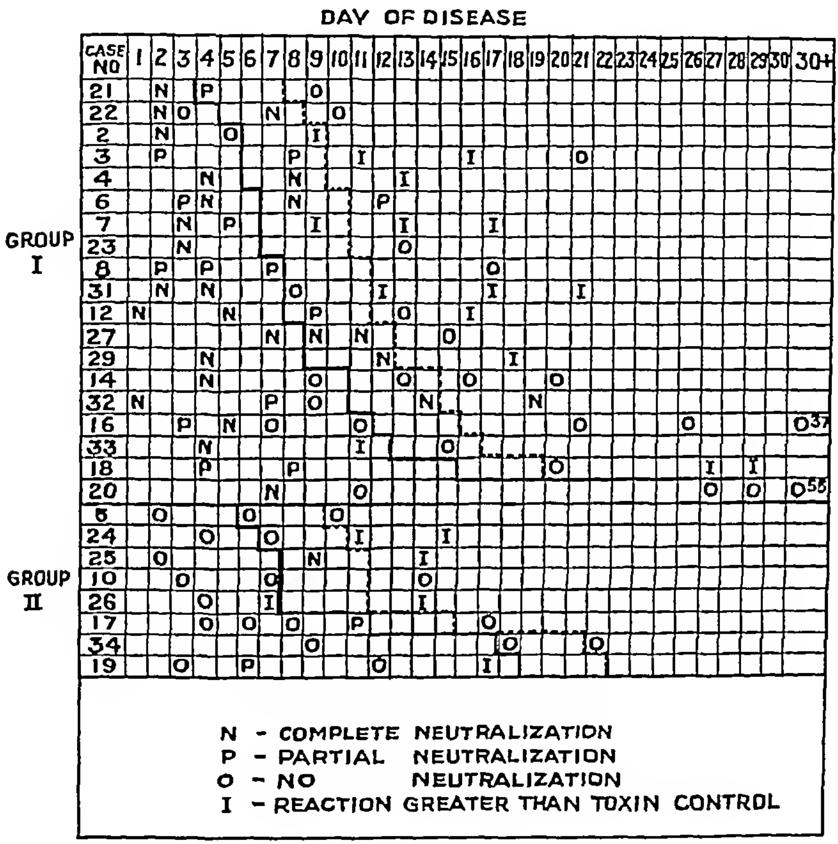

CHART 3 NEUTRALIZING CAPACITY OF THE SERUM OF ERYSIPELAS PATIENTS
Case numbers up to 27 agree with those of charts 1 and 2

were thoroughly shaken and heated at 37°C for one hour One-tenth cubic centimeter of each mixture was injected into the skin of individuals reactive to 1 S T D of filtrate In addition 1 S T D of the filtrate alone was injected at the same time for comparison

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DAY OF DISEASE

	CASE NO	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	30+
GROUP I	21		N		P					O																						
	22		N	O				N			O																					
	2		N			O				I																						
	3		P						P			I					I					O										
	4				N				N					I																		
	6			P	N				N				P																			
	7			N		P				I				I				I														
	23			N										O																		
	8		P		P			P										O														
	31		N		N				O				I					I				I										
	12	N				N				P				O			I															
	27							N		N		N				O																
	29				N								N						I													
	14				N					O				O			O				O											
	32	N						P		O					N					N												
	16			P		N		O				O										O					O					O37
	33				N							I				O																
	18				P				P												O							I		I		
	20							N				O																O		O		O55
GROUP II	5		O				O				O																					
	24				O			O				I				I																
	25		O							N					I																	
	10			O				O							O																	
	26				O			I							I																	
	17				O		O		O			P						O														
	34									O									O				O									
	19			O			P						O					I														

N - COMPLETE NEUTRALIZATION
P - PARTIAL NEUTRALIZATION
O - NO NEUTRALIZATION
I - REACTION GREATER THAN TOXIN CONTROL

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DISCUSSION

The three important phenomena brought to light in the preceding observations, namely, the tendency for the cutaneous reactivity of erysipelas patients to become more marked during convalescence the absence of a demonstrable toxin in the circulating blood of patients in the acute stage of the disease, and the neutralization of erysipelas streptococcus culture filtrates by the serum of most patients in the acute phase of the disease with apparent loss of this power during convalescence, fail to support Birkhaug's concept of erysipelas as a specific toxemia, recovery from which is due to the development of an antitoxic immunity

The results of the skin tests suggest, rather, that an increasing sensitiveness or allergy to streptococcus products, presumably liberated at the site of the erysipelatous lesion, develops with the progress of the disease to convalescence and recovery The fairly definite correlation between the rapidity with which skin reactivity developed and the clinical course of the disease, as shown in chart 2, furthermore suggests that the development of tissue allergy may play at least a part, perhaps an important part, in the mechanism of recovery from the infection That the skin reactions were neutralizable not only in sensitive normal individuals but also in sensitive patients in the convalescent period, as proved to be the case on a number of tests, is not surprising, since it has been shown by Dochez and Stevens (10) that the skin reactions of rabbits rendered allergic to undiluted culture filtrates of erysipelas streptococci, are neutralizable during the early phase of sensitivity

The negative results of the tests for toxin in the circulating blood early in the disease indicate that a specific toxemia in the sense in which it has been shown to occur in scarlet fever (9), plays little or no significant part in erysipelas This view is further supported by the neutralization tests, in which it is shown that the majority of adult patients with erysipelas already possess early in the disease sufficient circulating antibody to neutralize 20 S T D of filtrate per cubic centimeter of blood The toxigenic activity of erysipelas streptococci, in most instances relatively poorly developed as compared with that of most scarlatinal streptococci, is probably counteracted at the

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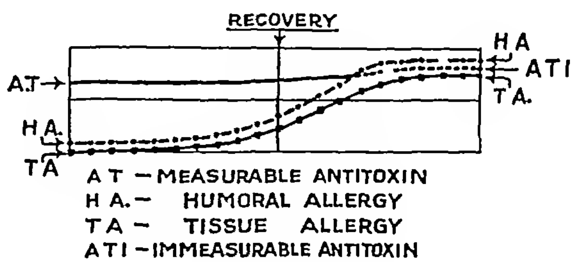

FIG 1 DEVELOPMENT OF IMMUNITY STATES IN ERYSIPELAS

At the point at which the line H A crosses the line A T the neutralization of toxin is obscured and the antitoxin becomes immeasurable

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If, then, it be assumed that the rate of development and degree of tissue allergy as measured by the skin tests, of antitoxic immunity as measured by the neutralization tests, and of humoral allergy as measured by the apparent loss of the neutralizing capacity of the serum, are variable and mutually independent, any variation in the results can be explained To do so in each case would be impossible within the limits of this report The most frequent relationship and

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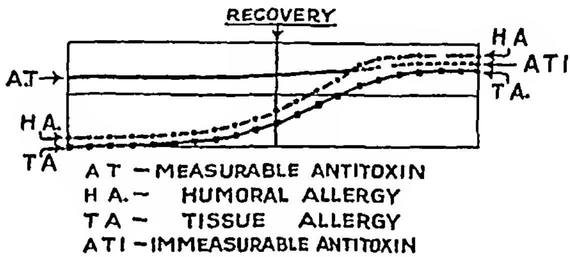

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The relations between systemic blood pressure and the cardiac output per minute and per beat is of interest and the administration of atropine affords an opportunity to study these relations also The effect of atropine on systemic blood pressure has been studied by Harris (5) in normal adults and by Sturgis, Wearn and Tompkins (6) in patients with "effort syndrome" Harris observed that the subcutaneous injection of 1 2 mgm of atropine was followed by a fall in systolic pressure and a decrease in the pulse pressure He inferred that the output of the heart was diminished A similar decrease after a similar dose was found by Sturgis, Wearn and Tompkins (6) in patients with effort syndrome

Many studies have been made of the effect of atropine on the heart rate It is important to note that doses of different magnitude may have opposite effects on the heart rate As pointed out by McGuigan (7) small doses (0 4 to 0 6 mgm) may decrease the rate or leave it unchanged while a dose of 1 2 mgm usually suffices to increase it considerably

METHODS

Observations on the cardiac output, heart rate, metabolic rate, and systemic blood pressure were made before and after the intravenous injection of 1 2 mgm of atropine sulphate In a preliminary experiment 2 4 mgm were injected but this amount rendered the subject so restless and uncomfortable that the observations were not comparable with those made before the injection when the subject was quiet and at ease

The output of the heart was measured by the method of Field, Bock, Gildea and Lathrop (8) All observations were made in the morning with the subject having had no food for at least 12 hours and after he had rested 30 to 45 minutes in the reclining position, in which he remained while the observations were made Each subject was trained in the necessary respiratory manoeuvers before the cardiac output was actually measured Then a preliminary measurement was made and if the subject showed himself well trained the complete experiment was carried out on the following day The order of procedure was as follows first the samples of alveolar and "mixed venous" gases were collected, then the expired air was collected for a six minute period, and finally the blood pressure was taken At short intervals during these observations the pulse was counted These counts were averaged and the result is designated the "average pulse rate"

When this control observation was completed 1 2 mgm of atropine sulphate were given intravenously and the observations immediately repeated, with the addition of several measurements of the blood pressure during the procedure

A third series of observations was made 1 to 1½ hours after injection of atropine

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The effect of injecting atropine upon the pulse rate, respiratory quotient, metabolic rate, excretion of CO_2, arterio-venous difference, and cardiac output per minute and per beat

	Average pulse rate	Respiratory quotient	Basal metabolic rate	CO_2 excreted per minute	A V difference	Cardiac output per minute	Cardiac output per beat
			per cent	*cc*	*volumes per cent*	*cc*	*cc*
Subject 1 (W G)							
March 17, 8 30 a m	72	0 81	−14	181	3 11	5,820	81
March 18, 9 30 a m.	67	0 80	−15	178	3 15	5,650	84
March 18, 10 10 a m *	110	0 80	−12	185	2 60	7,110	65
March 18, 11 20 a m.	85	0 83	−17	177	2 52	7,020	83
Subject 2 (F N)							
March 24, 8 30 a m.	76	0 76	+2	193	3 61	5,350	70
March 25, 8 45 a m.	79	0 79	+0	191	3 96	4,820	61
March 25, 9 42 a m.*	112	0 72	−2	179	2 84	6,300	56
March 25, 11 00 a m	84	0 76	−8	174	2 88	6,040	72
Subject 3 (T A)							
March 31, 8 30 a m.	65	0 81	−15	182	4 62	3,940	60
April 1, 10 40 a m *	93	0 78	−11	186	3 65	5,100	55
April 1, 11 48 a m.	75	0 79	−14	179	3 32	5,390	72
April 10, 8 30 a m.	62	0 89	−15	189	4 37	4,320	70
Subject 4 (M H)							
April 14, 8 30 a m.	64	0 83	−13	198	5 01	3,950	62
April 15, 8 15 a m.	61	0 84	−12	203	5 02	4,040	66
April 15, 9 15 a m *	91	0 84	−12	199	4 62	4,300	47
April 15, 10 36 a m.	74	0 82	−14	191	3 72	5,140	69
Subject 5 (C K)							
April 22, 8 30 a m.	71	0 84	−19	177	4 10	4,320	61
April 23, 9 00 a m.	65	0 86	−16	185	4 74	3,900	60
April 23, 10 19 a m.*	115	0 86	−20	176	5 15	3,420	30
April 23, 11 50 a m.	81	0 84	−25	162	5 06	3,200	40
Subject 6 (C B)							
May 6, 8 00 a m.	63	0 87	−17	173	3 73	4,650	74
May 6, 9 00 a m.*	104	0 76	−14	160	2 90	5,520	53
May 6, 10 20 a m.	76	0 74	−21	144	3 27	4,400	58
May 6, 11 50 a m.	66	0 77	−15	158	3 45	4,580	69

* 1 to 2 minutes before this time the subject received an intravenous injection of 1 2 mgm. atropine sulphate Immediately thereafter the determination of the cardiac output was begun

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The metabolic rate

No constant change in the metabolic rate was observed following the administration of atropine In fact, the average rates just before and just after injection were identical As is usual with trained subjects the basal rates are uniformly low The respiratory minute volume increased on the average 4 per cent, which fits in with the absence of change in metabolic rate

The blood pressure

It is realized that figures for the diastolic pressure are not accurate because of the difficulty of recognizing the diastolic point by the usual criteria This difficulty we attempted to minimize by having all

TABLE 2

Percentage changes in pulse rate and cardiac output per minute and per beat following the injection of 1 2 mgm atropine sulphate intravenously

	Subject						Average
	1	2	3	4	5	6	
Pulse rate per minute	+57	+45	+46	+45	+69	+65	+56
Cardiac output per minute	+24	+24	+23	+8	−17	+19	+14
Cardiac output per beat	−22	−15	−15	−27	−51	−28	−26

pressures taken with the same mercury manometer and by the same observer Even so, successive observations sometimes showed a striking lack of agreement Our observations on the effect of atropine on the blood pressure are summarized in tables 3 and 4

Table 3 shows the blood pressure reading just before and for some twenty minutes after the administration of the drug, with simultaneous pulse rates It emphasizes the striking lack of correlation between heart rate and blood pressure in that the former may nearly double without change in the latter In two instances there was a definite rise in both systolic and diastolic pressures

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95 to 110 mm This range of pressure is that usually found in healthy young men under standard basal conditions

DISCUSSION

The administration of atropine, according to these observations, increases the rate of the heart relatively much more than the output of the heart per minute and thus produces a diminution in the output of the heart per beat This fact emphasizes the importance of the filling of the heart in relation to its output, and thus the importance of the factors determining the venous pressure These factors include gravity, the aspirating action of the thorax and the contraction of the muscles of the body as well as the pumping force of ventricular systole Atropine has, of course, effects other than acceleration of the heart

TABLE 4

The pulse pressure (in millimeters of mercury) before and after the intravenous injection of 1 2 mgm atropine sulphate Each figure represents the average of several measurements

	Subject						Average
	1	2	3	4	5	6	
Before atropine	31	38	28	38	35	37	34 5
Immediately after atropine	25	44	40	34	30	33	34 3
1 to 2 hours after atropine	30	45	27	28	32	30	32 0

These include according to Cushny (9) a sedative action on many organs containing unstriped muscle, a decrease of most secretions, and a stimulation of the central nervous system, particularly the motor divisions of the brain These effects, particularly the last, which is presumably responsible for the restlessness sometimes observed in our experiments, may possibly affect the filling of the heart and thus account for the small but definite increase which was observed

The oxygen consumption of the resting human heart, according to Bainbridge (10) is about 12 5 cc per minute This amount is approximately 5 per cent of the total oxygen consumption of the body per minute This being true small changes in the work of the heart can hardly be recognized by changes in the total oxygen consumption The unchanging metabolic rate in these experiments cannot be taken as evidence that the work of the heart was not increased

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at 1½ hour intervals on January 31, 1927 in which the variation in the output of the heart was only 100 cc

This general agreement constitutes not only a demonstration of the degree of perfection of physiological regulation but also impressive evidence of the agreement in this subject, of two quite different methods of measuring the output of the heart

TABLE 1

The output of the heart per minute and related figures

Date	Method	Pulse rate	Basal metabolic rate	Respiratory quotient	Oxygen per minute	Carbon dioxide per minute	Arterio venous difference oxygen	Arterio-venous difference carbon dioxide	Output per beat	Output per minute
			per cent of normal		*cc*	*cc*	*volumes per cent*	*volumes per cent*	*cc*	*cc*
March 31, 1923	Burwell and Robinson	67	−10	0 78	238	186	6 44	5 02*	59	3,700
April 17, 1923	Burwell and Robinson	66	−8	0 85	236	200	5 91	5 02*	60	3,940
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January 31, 1927										
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June 24, 1927	Bock et al	71	−7	0 82	243	199	5 16*	4 23	66	4,700
February 10, 1928	Bock et al.	65	−8	0 83	231	192	6 38*	5 29	56	3,630

* Calculated

Why three successive measurements during ten days in June 1927 should have given higher figures than any other of the thirteen is not known The weather at this period was warm but the tempera-

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normal level In this respect, it is similar to a slow change in the myxedematous condition of the tissues

The change appears to persist as long as the metabolism is held at a normal level by the administration of thyroid extract

TABLE 1

Case number	Name	Age	Laboratory number	Before administration of thyroid extract: Basal metabolic rate	Before administration of thyroid extract: Concentration of protein* in spinal fluid	After administration of thyroid extract: Basal metabolic rate	After administration of thyroid extract: Concentration of protein* in spinal fluid
				per cent of normal	*mgm per 100 cc*	*per cent of normal*	*mgm per 100 cc*
1	Mr J G	53	4236	−26	221	−3	49
2	Mrs J W	50	4224	−21	129	+2	58
3	Mr H L	21	4302	−34	111	+19	30
4	Mrs M V L	47	3984	−17	93	+23	32
5	Mrs M B	30	4533	−40	80	−12	43
6	Mrs L C	53	4532	−46	73	−10	32
7	Mrs E G	48	4671	−43	72	−9	36
8	Miss E MacD	43	4423	−24	72	±0	44
9	Mrs G M	33	4434	−27	65	+7	27
10	Mrs A J	33	4681	−28	61	−11	34
11	Mrs M LeB	43	3532	−24	58	+15	41
12	Mrs M B	57	1836	−24	48	−5	24
13	Mrs A H	48	1807	−22	46	+16	27
14	Mrs M H	35	4179	−28	38	+8	44
15	Mrs D B	51	4339	−25	34	+17	21
16	Mrs M M	53	4651	−29	34	+6	22
17	Miss J W	47	2680	−22	28	±0	31

The cell count was normal throughout

In most of the cases each figure represents the average of two or more determinations made on different days

*The determinations were made on the first 2 to 3 cc. of fluid removed from the lumbar region

The protein content of the fluid obtained after withdrawing large quantities from the lumbar region (60 to 90 cc), was much greater than is found normally under these conditions, and was sometimes only slightly less than that of the first 2 cc removed This finding indicated that the protein content of cerebral fluid was greater than normal, a supposition that was supported by obtaining cistern

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J G (case 1) had myxedema or a brain tumor The latter diagnosis was seemingly corroborated by the finding of a high pressure as well as a high concentration of protein in the spinal fluid His appearance was not characteristic of the full blown picture of myxedema While the diagnosis was in doubt, similar spinal fluid findings were obtained for the first time in several cases of typical myxedema Thyroid extract was, therefore, administered to J G and produced a well marked reduction in the concentration of protein, as well as a clinical cure

The cause of the high protein concentration in the spinal fluid is uncertain It is possibly related in some way to the storage of nitrogenous substances in myxedema (2) (3) It is of interest that an albuminuria is frequently present in this disease (2) (4) (5) This usually disappears or decreases markedly when thyroid is administered (5) The albuminuria and the high spinal fluid protein content may be, in part, manifestations of the same pathological condition, viz , an altered permeability of cell membranes throughout the body

SUMMARY AND CONCLUSIONS

The concentration of protein in the spinal fluid is high in most cases of myxedema, and usually drops to within normal limits when thyroid extract is administered

The high protein content both of cistern fluid and of fluid obtained after withdrawing large quantities from the lumbar region, indicates that the protein content of cerebral fluid is also high during the period of myxedema This finding suggests that the fluid which comes through the choroid plexus may have a greater protein concentration than normal

The knowledge that the concentration of protein in the spinal fluid is usually high in myxedema is of diagnostic value in rare instances in which this disease may be confused with brain tumor and chronic nephritis

We wish to thank Drs James B Ayer and Frank Fremont-Smith, whose interest in this and related problems made it possible to combine the research facilities of the metabolism and neurological labora-

J G (case 1) had myxedema or a brain tumor The latter diagnosis was seemingly corroborated by the finding of a high pressure as well as a high concentration of protein in the spinal fluid His appearance was not characteristic of the full blown picture of myxedema While the diagnosis was in doubt, similar spinal fluid findings were obtained for the first time in several cases of typical myxedema Thyroid extract was, therefore, administered to J G and produced a well marked reduction in the concentration of protein, as well as a clinical cure

The cause of the high protein concentration in the spinal fluid is uncertain It is possibly related in some way to the storage of nitrogenous substances in myxedema (2) (3) It is of interest that an albuminuria is frequently present in this disease (2) (4) (5) This usually disappears or decreases markedly when thyroid is administered (5) The albuminuria and the high spinal fluid protein content may be, in part, manifestations of the same pathological condition, viz , an altered permeability of cell membranes throughout the body

SUMMARY AND CONCLUSIONS

The concentration of protein in the spinal fluid is high in most cases of myxedema, and usually drops to within normal limits when thyroid extract is administered

The high protein content both of cistern fluid and of fluid obtained after withdrawing large quantities from the lumbar region, indicates that the protein content of cerebral fluid is also high during the period of myxedema This finding suggests that the fluid which comes through the choroid plexus may have a greater protein concentration than normal

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TABLE 1

Recovery from diabetic acidosis with the aid of insulin, water, and carbohydrate, but without salt, or alkali

Date	Time	Blood serum: BCl	BHCO$_3$	pH	Protein: By refractometer	Protein: By Kjeldahl	B-HPO$_4$	Lactic acid	Diacetic acid	Total base	Undetermined (ketone) acid	Glucose	N.P.N	Serum water	Osmotic pressure: Observed	Osmotic pressure: Calculated
Case 1 Eddie S																
		mM	*mM*		*grams per cent*	*grams per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	*mgm per cent*	*mgm per cent*	*grams per cent*	*mM*	*mM*
September 16, 1926	11 30 a m	84 8	4 7	7 00	9 99		3 2	2 5				488	37 8		351	
September 16, 1926	4 30 p m	79 2	6 0	7 13	9 13							121	39 8		291	
September 16, 1926	9 30 p m	90 0	7 2	7 18	8 71							78	46 2		285	
September 17, 1926	7 30 a m	90 0	14 2	7 23	8 49							91	41 8			
September 17, 1926	5 00 p m	87 0	14 0	7 38	8 28							70	42 0			
September 18, 1926	8 00 a m	80 0	15 8	7 35	7 85							259	66 0			
September 21, 1926	8 00 a m	80 4	21 4	7 38	7 63							430	50 0			
Case 2 Billy R																
June 3, 1926	11 30 a m	92 0	6 2	7 17	9 99							516	52 2			
June 3, 1926	4 00 p m	91 2	7 7	7 22	9 77							380				
June 3, 1926	9 00 p m											182				
June 4, 1926	8 45 a m	95 2	19 1	(7 35)	8 81		(3 0)	(2 0)		138	1 0	112	46 2			
June 5, 1926	8 45 a m	86 0	17 8		8 06							349	36 6			

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		mM	mM		grams per cent	grams per cent	mM	mM	mM	mM	mM	mgm per cent	mgm per cent	grams per cent	mM	mM
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June 5, 1926	8 45 a m	86 0	17 8		8 06							349	36 6			

TABLE 2

Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate and Ringer's solution, but without alkali

Date	Time	Blood serum: BCl	BHCO₃	pH	Protein: By refractometer	Protein: By Kjeldahl	B HPO₄	Lactic acid*	Diacetic acid*	Total base	Undetermined (ketone) acid	Glucose	N P N	Serum water	Osmotic pressure: Observed	Osmotic pressure: Calculated
Case 4 Loretta B																
		mM	mM		grams per cent	grams per cent	mM	mM	mM	mM	mM	mgm per cent	mgm per cent	grams per cent	mM	mM
January 24, 1927	11 45 a m	95 0	12 9	(7 30)	8 92		3 5	(2 0)	5 1	146	15	248	31 7			303
January 25, 1927	9 00 a m	96 5	5 4	(7 20)	9 13			(2 0)	7 4			386	29 6			
January 25, 1927	2 00 p m							(2 0)	7 7			297				
January 26, 1927	9 00 a m	98 7	5 9	(7 20)	9 99		3 3	(2 0)	8 0			457	36 8			
January 26, 1927	2 00 p m	102 0	7 0	7 25	9 77		3 2	(2 0)	8 4	147	14	300	40 0			309
January 27, 1927	9 00 a m	101 0	10 8	7 30	7 85		3 0	(2 0)	6 5	143	11	295	32 8			302
January 28, 1927	9 00 a m	96 0	13 2	7 34	7 63		(3 0)	(2 0)	5 8	143	13	297	34 4			300
January 29, 1927	9 30 a m				7 63			(2 0)	5 0			500				
February 4, 1927	9 00 a m	95 0	24 9	7 49	6 55		(3 0)	1 8	(0)	146	6	282	25 0			301
February 7, 1927	9 00 a m	96 0	25 4	7 49	6 55		(3 0)	1 4	(0)	144	4	56	(25 0)			274
Case 1 Eddie S																
April 15, 1927	11 00 a m	92 3	5 3	7 07	11 8		4 6	5 6	4 5	141	10	734	45 0		309	325
April 16, 1927	9 00 a m	95 3	16 2	7 35	8 06		2 5	2 1	2 2	135	3	29	38 0			273

( ) Assumed values

* Determined together in Case 4

TABLE 2

Recovery from diabetic acidosis with the aid of insulin, water, carbohydrate and Ringer's solution, but without alkali

Date	Time	Blood serum														
					Protein										Osmotic pressure	
		BCl	$BHCO_3$	pH	By refractometer	By Kjeldahl	B_2HPO_4	Lactic acid*	Diacetic acid*	Total base	Undetermined (ketone) acid	Glucose	N P N	Serum water	Observed	Calculated
Case 4 Loretta B																
		mM	*mM*		*grams per cent*	*grams per cent*	*mM*	*mM*	*mM*	*mM*	*mM*	*mgm per cent*	*mgm per cent*	*grams per cent*	*mM*	*mM*
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January 25, 1927	9 00 a m	96 5	5 4	(7 20)	9 13			(2 0)	7 4			386	29 6			
January 25, 1927	2 00 p m							(2 0)	7 7			297				
January 26, 1927	9 00 a m	98 7	5 9	(7 20)	9 99		3 3	(2 0)	8 0			457	36 8			
January 26, 1927	2 00 p m	102 0	7 0	7 25	9 77		3 2	(2 0)	8 4	147	14	300	40 0			309
January 27, 1927	9 00 a m	101 0	10 8	7 30	7 85		3 0	(2 0)	6 5	143	11	295	32 8			302
January 28, 1927	9 00 a m	96 0	13 2	7 34	7 63		(3 0)	(2 0)	5 8	143	13	297	34 4			300
January 29, 1927	9 30 a m				7 63			(2 0)	5 0			500				
February 4, 1927	9 00 a m	95 0	24 9	7 49	6 55		(3 0)	1 8	(0)	146	6	282	25 0			301
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centration was compensated for osmotically by urea increase In severe cases of acidosis of this type alkali administration seemed indicated and, together with salt administration, was at least partially effective in restoring the normal plasma electrolyte content and in promoting urea excretion

It is the object of this paper to present data obtained by studying, in a similar way, the composition of the plasma in cases of severe

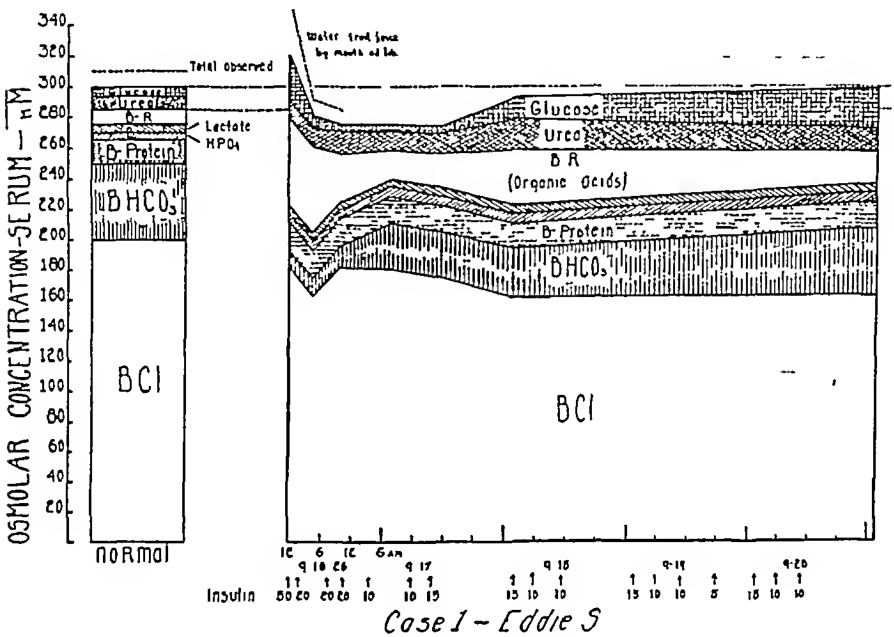

CHART 1 THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN AND CARBOHYDRATE

diabetic "acidosis," and the changes which occurred during recovery, when treatment consisted principally of administration of (*a*) *insulin* and *water*, with and without *carbohydrate,* (*b*) insulin, water, carbohydrate and *salt solution,* and (*c*) insulin, water, carbohydrate, salt solution and *alkali* From such a study it was hoped that a rough evaluation could be made, as far as their effect, at least, on the recovery of plasma $BHCO_3$ and pH is concerned, of *oxidation* of *organic acid, urinary excretion* of chloride bound to ammonia, and alkali

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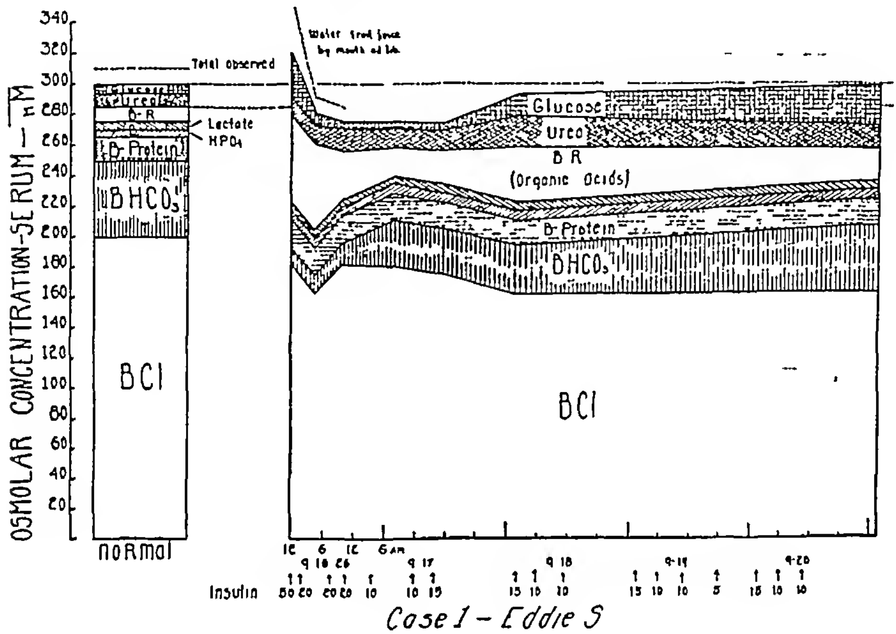

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least a roughly quantitative fashion in the same manner that lactic acid was determined [1]

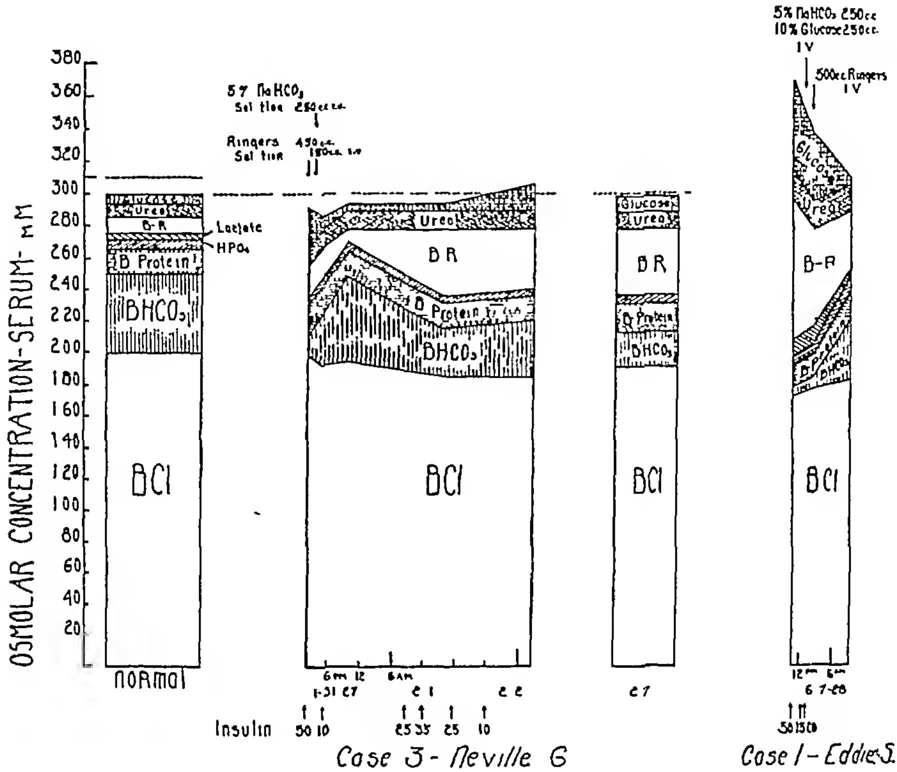

CHART 3 THE OSMOLAR ELECTROLYTE AND NON-ELECTROLYTE COMPOSITION OF THE PLASMA IN SEVERE DIABETIC ACIDOSIS, AND CHANGES TAKING PLACE AS A RESULT OF THE ADMINISTRATION OF WATER, INSULIN, CARBOHYDRATE, SALT SOLUTION AND ALKALI

In estimating the concentration of the total ketone acids, the sum of the principal normal acids ($Cl' + HCO_3' +$ protein$' + HPO_4''$

[1] By titrating as rapidly as possible the bisulfite freed from combination with acetaldehyde and acetone, lactic acid and diacetic acid together were determined Lactic acid alone was then determined in the usual manner after preliminary distillation in acid solution of preformed acetone and diacetic acid, the distillate being caught in Scott-Wilson reagent and furnishing a rough check on the value obtained by titration difference

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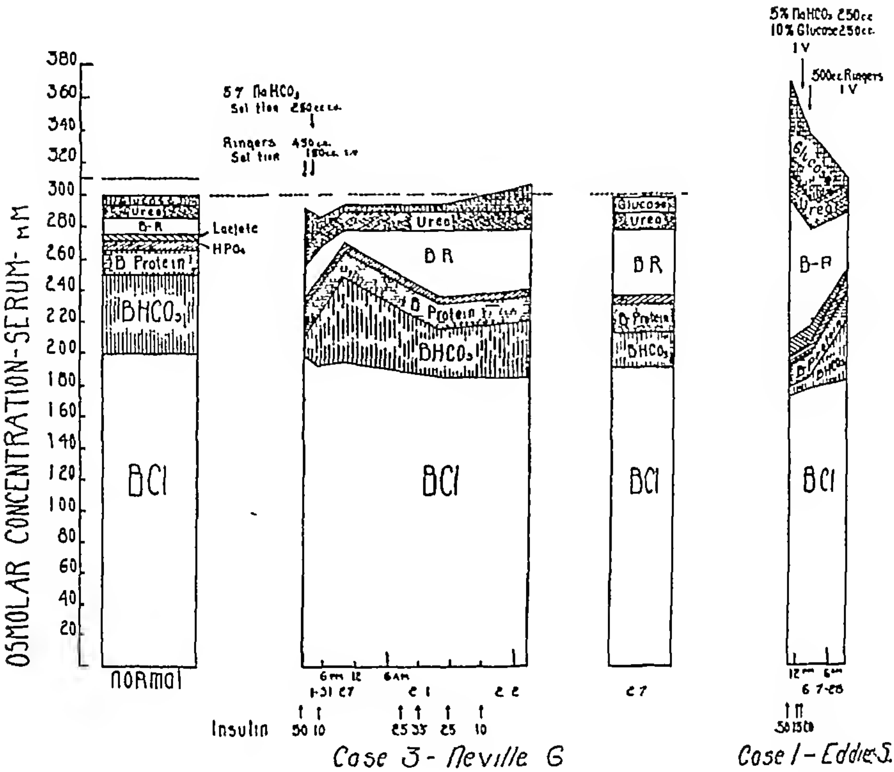

Chart 3 The Osmolar Electrolyte and Non-Electrolyte Composition of the Plasma in Severe Diabetic Acidosis, and Changes Taking Place as a Result of the Administration of Water, Insulin, Carbohydrate, Salt Solution and Alkali

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April 16, 1927 6 00 a m Insulin 15 units subcutaneously
Admission of April 3, 1928 (table 3)
April 3, 1928
- 11 45 a m Insulin 40 units, intravenously
- 11 45 a m Insulin, 40 units, subcutaneously
- 11 45 a m 7 5 per cent glucose solution, 400 cc , intravenously
- 11 45 a m Ringer's solution, 400 cc , intravenously
- 11 45 a m 5 per cent sodium bicarbonate solution 500 cc , intravenously
- 3 00 p m Insulin, 50 units, subcutaneously
- 4 00 p m Ringer's solution by Murphy drip per rectum
- 9 00 p m Insulin 15 units subcutaneously

April 4, 1928
- 3 00 a m Insulin, 15 units, subcutaneously
- 9 00 a m Meal *P* 20, *F* 50, *CH* 20
- 9 00 a m Insulin 20 units, subcutaneously
- 12 30 p m Meal as above
- 12 30 p m Insulin 15 units subcutaneously
- 6 00 p m Meal as above
- 6 00 p m Insulin 15 units, subcutaneously

April 5, 1928 Meals and insulin as on April 4, 1928
Admission of June 6, 1928 (table 3)
June 6, 1928
- 11 45 p m Insulin 50 units intravenously
- 1 00 a m 500 cc 5 per cent Glucose solution containing 12 5 grams $NaHCO_3$ and 15 units insulin, intravenously

June 7, 1928
- 1 30 a m Ringer's solution 400 cc intravenously
- 1 30 a m Insulin 20 units subcutaneously
- 9 00 a m Previous diet and insulin dosage resumed

Case 2 Billie R This patient developed symptoms of diabetes mellitus in January, 1924, when 8 years of age During hospital admission in February, 1924, he was found to be a mild diabetic, showing no hyperglycemia on the usual diabetic diet without insulin After discharge from the hospital, dietary indiscretions were frequent, and gradually carbohydrate tolerance was lost, and daily insulin administration became necessary As punishment for one such lapse on June 1, 1926, he was put to bed without supper or insulin The next morning he complained of abdominal pain, felt nauseated and vomited Because he would not eat breakfast, insulin was again withheld Abdominal pain and nausea persisted, hyperpnea and drowsiness were noted and he was then brought to the hospital As in Case 1, leucocytosis of 40,000 without fever, was noted, and all symptoms disappeared when recovery from acidosis occurred (table 2)

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January 25, 1927
- 9 00 a m Insulin 50 units intravenously Ringer's solution per rectum by Murphy drip
- 3 25 p.m Insulin 35 units subcutaneously Orange juice 200 cc 4 per cent glucose per rectum as Murphy drip Orange juice 200 cc
- 8 00 p m Insulin 15 units subcutaneously

January 26, 1927
- 2 00 a m Insulin 15 units subcutaneously
- 9 00 a m 5 per cent glucose 1000 cc intravenously
- 9 30 a m Insulin 50 units intravenously
- 10 45 a m Insulin 50 units subcutaneously
- 12 45 p m Insulin 50 units subcutaneously
- 11 00 p m Ringer's solution 500 cc subcutaneously

January 27, 1927
- Insulin 125 units subcutaneously
- Ringer's solution 500 cc subcutaneously
- Regular diet

January 28, 1927 Insulin 110 units, subcutaneously, with full diet

Case 5 Frances H Diabetic symptoms were first noted in December, 1923, when he was 9 years of age Shortly afterwards he was admitted to the hospital, where he was found normal except for moderately severe diabetes After a temporary improvement, his carbohvdrate tolerance again diminished On March 1, 1927, he was admitted with alkalosis, following too vigorous treatment with alkali and insulin administered by his family physician Proper diet and insulin routine were frequently interrupted and he was admitted to the hospital again on December 5, 1927, with moderately severe acidosis (table 1) Therapy was as follows

December 5, 1927
- 10.20 p m 10 per cent glucose 500 cc intravenously Insulin 40 units intravenously
- 11 00 p m Insulin 40 units, subcutaneously

December 6, 1927 Usual diet and insulin

Case 6 James Y Diabetic symptoms were first noticed in June, 1926, when he was 13 years of age After hospital admission, he was found normal except for moderately severe diabetes and was given an adequate diet and insulin dosage He did well in the hospital and after discharge until he developed a respiratory infection, which resulted in severe acidosis on December 29, 1927 Therapy at that time was as follows

December 29, 1927
- 5 30 p m Insulin 35 units subcutaneously
- 9 00 p m 10 per cent glucose 250 cc intravenously
- 9 00 p m Insulin 13 units, intravenously

January 25, 1927

9 00 a m Insulin 50 units intravenously Ringer's solution per rectum by Murphy drip

3 25 p.m Insulin 35 units subcutaneously Orange juice 200 cc 4 per cent glucose per rectum as Murphy drip Orange juice 200 cc

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In the more severe cases, $BHCO_3$ may be but 5 mM (corresponding to about 12 vols per cent CO_2 content) and the pH may be 7 00 or less In most instances, increase in ketone acids more than accounts for such diminution of the bicarbonate ion In one case, however (Case 3, table 3) there was noted a 17 0 mM decrease in $BHCO_3$ with but an indicated 9 0 mM increase in ketone acid

Of the remaining acids, chloride is most regularly affected Its concentration is always below normal, sometimes by as much as 20 mM Occasionally lactic acid is significantly increased, as in Case 1 on April 3, 1928 (table 3) Phosphoric acid concentration tends to be elevated slightly, but such elevation is not significant from the standpoint of its base-binding capacity Increase in protein concentration, although sometimes very marked, usually increases but little the base bound to protein because of the fall in pH which accompanies the plasma concentration

From the osmolar viewpoint, we note a reduction in total electrolyte concentration, with an increase in glucose concentration sufficient to maintain a normal or a high osmotic pressure The initially highest observed total osmolar concentration as indicated by the freezing point depression was 394 mM and occurred in Case 1 on April 3, 1928 (table 3) In this instance the theoretical osmolar concentration was 354 mM, 84 per cent of which was contributed by electrolyte The least depression of the freezing point (309 mM) was noted in case 1 on April 15, 1927 (table 2) In this instance the theoretical osmolar concentration was 325 mM, electrolyte accounting for 82 2 per cent of it

Recovery resulting from the administration of water, insulin and carbohydrate

The results of therapy as indicated above can be seen in table 1 and chart 1[2] The outstanding feature is the rapid disappearance of blood sugar, frequently sufficient, even despite carbohydrate administration, to produce marked hypoglycemia, without the simultaneous return of $BHCO_3$ to anywhere near its normal concentration Thus in Case 1 on September 16, 1927 ten hours after the beginning of

[2] In constructing this chart, total base values, equivalent to the average found on other occasions, were assumed

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ance with the Donnan principle of ionic and osmotic equilibrium, as shown by Van Slyke and his co-workers (4) to occur, but also into the fixed tissue cells, as suggested recently by Peters, returning to the plasma later as the hydrogen ion concentration of the cells diminished

It is of interest to note, however, that ultimately chloride *aids* in the recovery of plasma $BHCO_3$ In Case 1, for instance, it may be noted that as $BHCO_3$ increased from 14 2 mM on September 17, 1926 to 21 4 mM on September 21, 1926, BCl diminished from 90 0 to 80 4 mM This diminution of plasma chloride occurred after re-establishment of urinary secretion and during a time in which the hydrogen ion concentration of the plasma was diminishing It seems reasonable to assume, therefore, that when urinary secretion is re-established, $BHCO_3$ is supported by excretion of ammonium chloride into the urine

From such data as shown in table 1, therefore, we may conclude that administration only of water and insulin, with or without carbohydrate, restores but very slowly the $BHCO_3$ of the plasma, and therefore of the body fluids in general, the probable explanation being that as the hydrogen ion concentration of the fixed tissue cell decreases, the cell proteins claim base liberated from organic acid and chloride, the latter shifting into the plasma and claiming base originally held by organic acid, which otherwise might have combined with carbonic acid Later chloride may be further shifted into the urine, bound to ammonia and thus release base for combination with carbonic acid

With these points in mind, it should be of interest to note whether or not *salt solution* administration along with insulin, water, and carbohydrate, by causing an earlier and more intensive secretion of ammonium chloride into the urine causes a speedier restoration of plasma $BHCO_3$

The effect of salt administration

In Case 4 (table 2, chart 2) on January 24, 1927, during the first 48 hours of treatment consisting of administration of water, insulin, carbohydrate and Ringer's solution, "acidosis" actually became more marked, the plasma $BHCO_3$ falling from 12 9 to 5 9 mM During this interval, despite considerable insulin, little change in the blood sugar level was noted, and total organic acid concentration remained

ance with the Donnan principle of ionic and osmotic equilibrium, as shown by Van Slyke and his co-workers (4) to occur, but also into the fixed tissue cells, as suggested recently by Peters, returning to the plasma later as the hydrogen ion concentration of the cells diminished

It is of interest to note, however, that ultimately chloride *aids* in the recovery of plasma $BHCO_3$ In Case 1, for instance, it may be noted that as $BHCO_3$ increased from 14 2 mM on September 17, 1926 to 21 4 mM on September 21, 1926, BCl diminished from 90 0 to 80 4 mM This diminution of plasma chloride occurred after re-establishment of urinary secretion and during a time in which the hydrogen ion concentration of the plasma was diminishing It seems reasonable to assume, therefore, that when urinary secretion is re-established, $BHCO_3$ is supported by excretion of ammonium chloride into the urine

From such data as shown in table 1, therefore, we may conclude that administration only of water and insulin, with or without carbohydrate, restores but very slowly the $BHCO_3$ of the plasma, and therefore of the body fluids in general, the probable explanation being that as the hydrogen ion concentration of the fixed tissue cell decreases, the cell proteins claim base liberated from organic acid and chloride, the latter shifting into the plasma and claiming base originally held by organic acid, which otherwise might have combined with carbonic acid Later chloride may be further shifted into the urine, bound to ammonia and thus release base for combination with carbonic acid

With these points in mind, it should be of interest to note whether or not *salt solution* administration along with insulin, water, and carbohydrate, by causing an earlier and more intensive secretion of ammonium chloride into the urine causes a speedier restoration of plasma $BHCO_3$

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of ketone acid had occurred, $BHCO_3$ reached a high normal value, 26 1 mM In addition to this rapid and complete relief from acidosis, alkali administration had also the effect of diluting the plasma very rapidly, if we can judge from the refractometric values of protein

In Case 1, on June 6, 1928, extreme acidosis was present, $BHCO_3$ was but 3 0 mM and pH was less than 7 00 Despite immediate administration of insulin intravenously, no improvement was noted in two and one-half hours Alkali was then given, and there followed immediate clinical improvement and in seven and one-half hours plasma $BHCO_3$ was 22 9 mM and pH 7 43

Similar almost perfect chemical restitution of the plasma in 12 to 24 hours by means of combined insulin and alkali therapy was noted earlier in our experience (5) At that time, however, we were not as convinced as we are at present of the necessity of alkali in extreme cases of diabetic acidosis, and feared the development later of alkalosis It is very doubtful whether moderate alkalosis does any more harm than moderate acidosis, and certainly extreme alkalosis has been observed in cases of pyloric stenosis (6) with little in the way of alarming symptoms Similarly marked increase in plasma $BHCO_3$ developed in Case 1 on April 4, 1928, after combined insulin and alkali treatment without symptoms or apparent harm If tetany had occurred, we feel that it could easily have been controlled by inhalation of carbon dioxide and administration intravenously of calcium chloride We quite agree, however, that marked alkalosis should be avoided if possible and critical study of those cases who received alkali and developed alkalosis is indicated

Such a study, including observation of both blood and urine will be reserved for a later paper

In the meantime, however, we feel that cases of diabetic acidosis as severe as the cases described in this paper will be greatly benefited if, in addition to the usual water, insulin, carbohydrate and salt administration, alkali equivalent to one-fourth of that normally present in the body fluids is also administered For calculating such a dosage it is assumed that the body fluid comprises two-thirds of the body weight, and at its normal pH contains 3 0 grams of sodium bicarboate per liter

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The data reported herein are in terms of the percentage of weight, surface, and calories-per-hour above the corresponding values for persons of the same age and height, but of ideal weight

METHODS

The observations reported here were made on eight obese women normal except for their excess weight They were being reduced by dietary measures alone over periods varying from a few days to twenty weeks All of them were so

TABLE 1

Basal heat production in the obese

	Number of cases	Average calories per hour	Average basal metabolic rate
			per cent
Means (4)	10	81	0
Strouse and Wang (5)	10	74	+1
Present series	7	73	−3

intelligent and reliable that their adherence to the prescribed routine was not to be doubted In this series, there were three completed cases, three only partly reduced and two cases which have been observed for less than one month All of these patients carried on their usual activities throughout the dietary period

The diet was calculated on the basis of 1 gram of protein and 25 calories per kilogram of ideal weight Utilizing a FA/G ratio of 1 5, the grams of protein, carbohydrate, and fat were determined From these figures, the menu was made up including the protein and carbohydrate and omitting as much of the fat as possible This made possible diets with 600 to 650 calories total intake which was equivalent to 6 calories per kilogram actual weight in some of the patients studied

Basal metabolism determinations were done at intervals varying from a few days to two weeks using standard technique The Tissot apparatus was used and gas samples were analyzed in duplicate

The current insurance tables were used as standards of ideal weight (16) Surface area was calculated from the Boothby-Sandiford logarithmic chart (17)

A study of nitrogen balance in one patient of this series showed that the diet

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given kept her approximately in nitrogen equilibrium This observation and investigations in another series of cases to be reported later give reason to believe that all the patients maintained an approximate nitrogen balance during the period of dieting

OBSERVATIONS

The data presented are based upon 70 observations, 53 of which were made on the 5 cases which are considered as "reduced" The figures showing the status prior to dieting are the lowest values obtained before the diets began There is no evidence that the determinations were in any way unusual

A summary of our data appears in table 2 The averages of the initial data represent observations on all 7 cases For comparison

TABLE 3

Influence of diet on calories per hour

Case number	Outset	First month	Second month	Third month	Fourth month	Fifth month
1	69	65	63	62	53	52
2	70	68	63	64	63	
3	72	75	73	76	72	69
4	74	69	64	65	62	62
5	70	66	58	60		
Average	71	66	64	65	62	61

with the figures after reduction, the averages of the initial values for the 5 reduced cases are tabulated separately The influence of weight reduction is shown in the second part of the table These figures describe the metabolic status of each patient on the day of her last examination after the designated period of dietary restriction

The influence of dietary measures on the total calories per hour is indicated in table 3 which shows the average values for all determinations made during the given months

Eight observations have been made upon a woman 52 years of age who was only 25 per cent overweight at the outset Her surface was 11 per cent increased and the calories, 4 per cent above the ideal normal In 6 weeks, she was reduced to 7 per cent excess weight with corresponding surface but no significant change in total

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Relatively large weight changes amounting to 2 to 4 pounds a day are commonly met with in the obese This phenomenon is apparently explained by the variable capacity of fat deposits for water storage, a conception which is supported by Lauter's (3) statement that the water content of human fat may vary from 8 to 70 per cent These large water shifts give rise to a plateau-and-step type of weight curve during reduction which has been mentioned by Newburgh (4) and others and which we have repeatedly observed We do not, however, feel that this factor materially influences our data

That a loss of fat tissue rather than a shifting water balance is responsible for the observed weight change is suggested by the following calculation "Gross" calories ingested are used instead of "net" calories in view of the relatively small energy fraction supplied by food The average basal calories per hour (table 3) plus 20 per cent is used as a measure of the total energy requirement (Mason (7)) Following the suggestion of DuBois (9) after Bozenraad, we estimate that 75 kgm of fatty tissue have 65 kgm of fat or 87 per cent fat

Basal calories per hour = 65
Basal calories per 24 hours = 1,560
Daily energy requirement—basal plus 20 per cent = 1870 calories

Average calories in diet = 620
1870 − 620 equals 1250 calories from fat
1250/9 3 equals 134 grams of fat equals 134 × 75/65 or 155 grams of fatty tissue per day
Average duration = 17 weeks or 119 days

$$\frac{155 \times 119 \times 2\ 2}{1000} \text{ equals } 40\ 6 \text{ pounds}$$

Weight loss observed = 41 pounds

On the basis indicated above, we have, therefore, accounted for nearly all of the gross observed weight loss

Surface changes

The significance of numerical values for body surface and surface changes depends upon the reliability of the method of estimation We have used tables based upon the DuBois formula which seems to be generally credited as the best available approximation even for the obese (3, 4, 10)

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Effect of weight reduction on energy exchange

If an obese patient may have a basal caloric requirement 30 per cent in excess of normal, it becomes important to know what happens to this excess when the weight is reduced If the basal calories do not change, the reduced person will have a metabolism comparable to that of a seriously toxic thyroid patient There is some evidence to indicate that the production of thyrotoxic symptoms by simple dietary reduction is not an impossibility (unpublished case)

In reviewing these data, the limits of normal variations in metabolism must be kept in mind Harris and Benedict (13) published data in 1921 showing the extreme variations of metabolism in a given person

TABLE 4

Excess of weight, surface and energy in the obese

	Number of cases	Age	Weight			Surface			Total basal calories per hour		
			Ideal	Observed	Excess	Ideal	Observed	Excess	Ideal	Observed	Excess
					per cent			*per cent*			*per cent*
Means	10	37	140	253	80	1 69	2 17	28	62	81	30
Strouse and Wang	10	27	125	207	66	1 57	1 95	24	59	74	25
Present series	7	37	129	238	83	1 59	2 06	29	58	73	26

Over a period of two years, a 14 per cent variation might be noted However, in a series of cases studied from one to three months, the coefficients of variation were around 4 per cent of the average metabolism DuBois (9) thinks that the variations in metabolism are smaller than the possible errors of the determinations

Acidosis causes an elevation in metabolism Mason (7) and others have found no evidence of clinical acidosis after the first few days of diet restriction in spite of the presence of acetone bodies in the urine This absence of clinical acidosis is in accord with our own experience

The average of our 5 cases shows a diminution of basal energy requirements of 240 calories or 14 per cent of the initial value Expressed in terms of the physiological status, these cases, which initially were metabolising 23 per cent in excess of normal, have

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Can this conclusion in regard to weight reduction in the obese apply to loss of weight in a normal person? Is the physiological reaction the same? For answer one might refer to the well-known work on this question of Benedict (14) and his collaborators which is briefly summarized below It is useful to distinguish three degrees of undernutrition, acute and chronic undernutrition, and starvation For comparison with our data one example of each type is taken from Benedict In tables 5 and 6, the figures for Squad A and B are taken from Lusk's (15) review of Benedict's work, and, in consequence, certain values differ very slightly from the original data of Benedict

In comparing ours with those of Benedict, it must be emphasized that his cases were healthy active males while our patients were

TABLE 6

Rates of change of weight, surface and energy

Group	Type	Subject	I Weight loss	II Surface loss	III Basal calories loss	IV Ratio Calorie loss / Weight loss	V Ratio Calorie loss / Surface loss
			per cent	*per cent*	*per cent*		
I	Acute	Squad B	6 5	<1 0	32 0	4 9	32 0+
II	Starvation	Leveran	17 0	5 0	30 0	1 7	6 0
III	Chronic	Squad A	8 5	3 3	19 0	2 2	5 9
IV	Obese		18 0	8 5	14 0	0 77	1 6

obese females They had at the outset physiologically normal basal metabolism, while that of this series was elevated 23 per cent

In regard to weight loss, none of the undernutrition cases approaches the magnitude of loss of our patients On a percentage basis, the starvation case lost a comparable amount

Clinically, the response in the two groups was entirely different, the undernourished groups became less ambitious, less energetic, tried to conserve all possible energy They were depressed, irritable, and unstable In contrast to this, the obese cases showed consistently more initiative, had a desire to do things, and felt in all respects better than for years previously

The physiological reaction is different in the different groups of cases The first two dropped 30 per cent of their calories in three

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No difference in quality of reaction was noted in the response of the so-called "endocrine" obesity patients and the "over-eating" cases There appears to be a difference in quantity of reaction due, perhaps, to the tendency of the former type to approach the theoretical basal metabolism more rapidly in proportion to weight loss than in the second type The weight loss continues in all cases to be directly proportional to the degree of deficiency of exogenous calories

CONCLUSIONS

1 The energy exchange in the obese, when compared to what would be normal for them, if on proper weight, is increased

2 This increase in energy exchange is of the same magnitude as the surface area increase beyond that normal for them

3 When obese patients are reduced by dietary measures alone, the energy exchange diminishes proportionally much more than the weight, or surface area

4 In spite of this drop in basal calories the metabolism never goes below limits normal for proper weight

5 This observation contrasts strikingly with the extreme energy economy in the individual of normal weight who is reducing by diet, as is shown by a comparison with Benedict's figures

6 There is, therefore, no evidence of an energy economy in the obese

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through glucose, which it has been shown requires insulin in its metabolism It has been shown that if the triose normally appears in the blood the amount must be exceedingly minute (5), that, when administered, it disappears from the blood coincident with the appearance of extra glucose (6, 7), that it cures insulin hypoglycemia (6), which only certain hexoses can do, that when administered to depancreatized dogs on a fixed diet and insulin, the same amount of glucose is excreted in the urine as when glucose itself is fed (7), that the fasting depancreatized dog excretes the same amount of extra glucose as is equivalent to the weight of triose fed (7), that the respiratory quotient of a fasting depancreatized dog is not affected by the administration of the triose (7), and that in the eviscerated animal the dihydroxyacetone does not cure the hypoglycemia nor disappear from the blood as does glucose but, in the absence of the liver, remains unchanged, and that most of the substance can be obtained from the muscles as the unchanged triose (9)

These investigations, however, did not include any evidence as to the behavior of the total metabolism of a fasting *normal* dog when given glucose or dihydroxyacetone The protocols later presented are of interest in supplying this information under experimental conditions, which have not been quite duplicated in man and from which further deductions may be drawn These observations were undertaken in the period November 1 to 16, 1926 From the December number of the Proceedings of the Society for Experimental Biology and Medicine we learned that Himwich, Rose and Malev (10) had presented a preliminary note on a somewhat similar experiment on December 15, 1926 Since, so far as we know, no more extensive report by these authors has appeared in the past year it seems desirable to place these observations on record

Himwich, Rose and Malev, using a trained dog, injected 10 grams of glucose or dihydroxyacetone dissolved in warm water subcutaneously and collected the expired air at short intervals through a leakproof mask into a spirometer whence samples were collected over mercury and analyzed by the Haldane-Henderson apparatus Prompt increases in the respiratory quotient occurred, the latter rising, in fact, over 1 0 in all experiments with dihydroxyacetone and in one case to 1 31 In the glucose experiments the respiratory quotient increased,

through glucose, which it has been shown requires insulin in its metabolism It has been shown that if the triose normally appears in the blood the amount must be exceedingly minute (5), that, when administered, it disappears from the blood coincident with the appearance of extra glucose (6, 7), that it cures insulin hypoglycemia (6), which only certain hexoses can do, that when administered to depancreatized dogs on a fixed diet and insulin, the same amount of glucose is excreted in the urine as when glucose itself is fed (7), that the fasting depancreatized dog excretes the same amount of extra glucose as is equivalent to the weight of triose fed (7), that the respiratory quotient of a fasting depancreatized dog is not affected by the administration of the triose (7), and that in the eviscerated animal the dihydroxyacetone does not cure the hypoglycemia nor disappear from the blood as does glucose but, in the absence of the liver, remains unchanged, and that most of the substance can be obtained from the muscles as the unchanged triose (9)

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total gaseous exchange in any one period and, therefore, figures on heat production per hour have been omitted It should also be stated that the behavior of the animals was very satisfactory The

TABLE 1

Period	O_2 absorption	CO_2 elimination	R Q	O_2 per kgm hour	Remarks
November 1, 1926 Dog A White wire-haired terrier Weight 6120 grams Last previous feeding October 30, 9 00 a m					
	cc	*cc*		*cc*	
8 55– 9 55 a m	4,566	3,485	0 76	746	Quiet Very quiet
9 55–10 55 a m	4,192	3,073	0 733	685	Slight movements Very quiet
11 05 a m					Electric power off
11 50 a m					25 grams glucose in 150 cc water
12 15– 1 15 p m	4,572	3,719	0 814	747	Very quiet Sitting up Quiet 3 movements
1 15– 2 15 p m	4,150	3,595	0 866	678	Occasional movement
2 15– 3 15 p m	3 644	3 078	0 845	595	Quiet Dog fed 4 00 p m
November 3, 1926 Same dog Weight 6000 grams Last previous feeding November 1, 4 00 p m					
8 35– 9 35 a.m	4,563	3,340	0 732	760	Quiet Very quiet
9 35–10 35 a m	4,074	3,144	0 772	679	Very quiet
10 45 a m					25 grams dihydroxyacetone
11 10–12 10 p m	4,032	3,969	0 984	672	Very quiet
12 10– 1 10 p m	3,796	3,001	0 896	633	Very quiet
1 10– 2 10 p m	3,745	3,139	0 838	624	Very quiet
2 10– 3 10 p m.	3,707	2,943	0 794	618	

movement recorder, as well as visual observation of the animal, permits us to state that in no case was it responsible for any significant oxygen utilization after the preliminary control period (not shown) was com-

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that it was receiving 20 grams of glucose in each experiment this animal seventeen control hours show an average oxygen consu tion per kilogram hour of 573 cc while the average oxygen consu tion per kilogram hour for the three hours following administrat of glucose was 554 cc, a negligible difference The animal, on c

TABLE 3

Period	O_2 absorption	CO_2 elimination	R Q	O_2 per kgm hour	Remarks
November 4, 1926 Dog B Wire haired terrier Weight 6,200 grams Las previous feeding November 2, 4 00 p m.					
	cc	cc		cc.	
8 30– 9 30 a m	4,159	2,982	0 717	591	Moving occasionally
9 30–10 30 a.m	3,458	2,676	0 774	495	Quiet
10 32 a m					25 grams glucose
10 45–11 15 a m	2,373	1,872	0 789	746	Fairly quiet
11 15–11 45 a m.	2,091	1,827	0 874	674	Quiet
11 45–12 15 p m	1,889	1,740	0 921	610	Very quiet
12 15–12 45 p m	1,940	1,715	0 884	626	Very quiet
12 45– 1 45 p m	3,847	3,063	0 796	620	Quiet
1 45– 2 45 p m	3,457	2,679	0 775	558	Movements slight
2 45– 3 45 p m	3 503	2,554	0 729	565	Quiet
November 10, 1926 Same dog Weight 5960 grams Last previous feeding November 8, a m					
8 25– 9 25 a m	3,276	2,768	0 753	550	6 movements, then quie
9 25–10 25 a m.	2,910	2,267	0 779	488	Fairly quiet
10 32 a m.					25 grams dihydroxyt tone
10 45–11 15 a m	1,485	1,628	1 10	498	Quiet
11 15–11 45 a m	1,833	1,593	0 869	616	Moving
11 45–12 15 p m.	1 903	1 796	0 944	638	Moving considerably
12 15–12 45 p m	1,800	1,412	0 784	604	Quiet
12 45– 1 45 p m.	2,698	2,137	0 792	453	1 slight movement
1 45– 2 45 p m	3,122	2,312	0 741	524	Moving

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TABLE 3

O_2 consumption, cubic centimeters per kilogram hour

Animal	Date	First control hour	Second control hour	First hour	Second hour	Third hour	Fourth hour
			1 Glucose tests				
A	November 1	746	695	747	678	595	
A	November 16	506	516	494	520	542	454
B	November 4	591	495	720	618	620	558
B	November 15	495	480	482	517	553	492
Average		584	546	611	608	602	501
			2 Dihydroxyacetone tests				
A	November 3	760	679	672	633	624	618
A	November 9	629	597	653	689	583	603
B	November 10	550	488	557	621	453	524
B	November 12	527	515	572	594	506	485
Average		616	570	588	627	541	557

	cc per kgm hour
Average of 16 control periods	579
Average of 15 post glucose periods	580
Average of 16 post dihydroxyacetone periods	578

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independently of actual combustion of a food administered and we must, therefore, conclude that such temporary changes in oxygen consumption as may occur are probably associated with such intermediary processes, e g , formation of fat, work expended by the liver in transforming the triose into glucose, kidney work, etc , or to another very important mechanism—the additional muscular work required in carrying on hyperventilation

While, as has been shown above, the total respiratory exchange is practically unchanged from the basal during the whole period of observation there are changes in oxygen consumption during the individual test periods (table 5) These, however, do not necessarily correspond with the alterations in the so-called respiratory quotient In fact, as table 6 shows, the highest CO_2 output occurs in the first half-hour or hour after triose administration while the oxygen consumption (table 5) is greatest in the second hour The ratio of CO_2 elimination to oxygen uptake (table 7) is consequently decidedly different from that occurring after glucose administration, in which case the rise in respiratory quotient is less abrupt and more prolonged Considering the data in tables 1 to 4 together with that of other workers, one is struck by the frequency with which the so-called respiratory quotient exceeds 1 0 Even holding the view that the respiratory quotient is an expression of dynamic equilibrium in food stuffs transformed, burned or stored, such ratios cannot be explained as due to combustion of carbohydrate alone but must include the formation of fat, and calculations of carbohydrate consumption based thereon must be in error Since, however, the oxygen intake is not decreased but the initial rise in the CO_2/O_2 ratio is due to additional CO_2 elimination, fat production does not appear to furnish a probable explanation for the sequence of events While it appears inherently improbable that combustion would occur in isolated stages, it may be pointed out that the change from sugar to lactic acid is anaerobic and requires no oxygen and produces no CO_2 It would appear then that any additional energy expenditure is required for some other purpose and that such expenditure is accompanied by CO_2 production in the absence of oxygen or that hyperventilation is the cause of the excess CO_2 production, or that both these processes take place in differing proportions It is again significant that the total oxygen intake after

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Examination of the data (1, 2, 4, 5) indicates that hyperventilation has taken place and a cause for this is of interest Increased oxygen consumption occurring later can then be explained on the basis of

TABLE 1

Dihydroxyacetone tolerance tests

Case	Time	Blood glucose	Blood dihydroxy acetone	Blood lactic acid	CO_2 combining power
		mgm per cent	*mgm per cent*	*mgm per cent*	*volumes per cent*
1	Fasting	85	0	18	58*
	30 minutes	90	17 5	50	52
	1 hour	90	15 8	40	60
	2 hours	95	13 2	26	59
	3 hours	95	8 8	23	62
2	Fasting	100	0	17	64
	30 minutes	120	13 2	24	56
	1 hour	135	8 8	21	52
	2 hours	100	8 8	18	61
	3 hours	80	4 4	11	63
3	Fasting	80	0	11	67
	30 minutes	110	45 5	31	60
	1 hour	85	28 0	26	63
	2 hours	65	8 8	19	67
	3 hours	85	4 4	9	67
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	30 minutes	80	8 8	38	60
	1 hour	60	4 4	33	56
	2 hours	85	1 8	15	59
	3 hours	80	0	17	63
5	Fasting	100	0	12	67
	30 minutes	100	26 3	37	59
	1½ hours	75	13 2	31	66
	2½ hours	80	8 8	23	65
6	Fasting	85	0	16	68
	30 minutes	105	17 5	42	58

* First blood hemolyzed

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respiratory quotient to rise above 1 0 and similar claims have been made for it in diabetic treatment, it was included in the investigation along with cane sugar, which splits into glucose and fructose Maltose, lactose, glucose and galactose, examples of aldoses, and the triatomic alcohol, glycerine, were selected for comparison with the above mentioned sugars

TABLE 3

Sucrose tolerance tests

Case	Time	Blood glucose	Blood fructose	Blood lactic acid	CO_2 combining power
		mgm per cent	*mgm per cent*	*mgm per cent*	*volumes per cent*
13	Fasting	105	0	17	63
	30 minutes	150	15 6	23	59
	1 hour	190	21 0	25	54
	2 hours	145	15 6	24	60
	3 hours	110	0	17	60
14	Fasting	95	0	28	60
	30 minutes	115	0	29	61
	1 hour	85	0	24	62
	2 hours	85	0	24	61
	3 hours				63
15	Fasting	100	0	10	65
	30 minutes	175	15 6	15	59
	1 hour	150	10 4	17	61
	2 hours	95	10 4	11	62
	3 hours	65	0	9	65
16	Fasting	100	0	11	61
	30 minutes	120	5 2	12	59
	1 hour	155	10 4	17	56
	2 hours	130	5 2	11	60
	3 hours	95	0	10	61

Disturbance of the acid alkali balance is perhaps the most potent cause of hyperventilation, and for its measurement the CO_2 combining power (Van Slyke's precision method (6)) was employed For certain reasons which will be discussed later the change encountered cannot be the maximal one, but it is sufficiently great to exceed many times the possible error The origin of the change in CO_2 combining power which preliminary tests showed to be present was not far to

respiratory quotient to rise above 1 0 and similar claims have been made for it in diabetic treatment, it was included in the investigation along with cane sugar, which splits into glucose and fructose Maltose, lactose, glucose and galactose, examples of aldoses, and the triatomic alcohol, glycerine, were selected for comparison with the above mentioned sugars

TABLE 3

Sucrose tolerance tests

Case	Time	Blood glucose	Blood fructose	Blood lactic acid	CO_2 combining power
		mgm per cent	*mgm per cent*	*mgm per cent*	*volumes per cent*
13	Fasting	105	0	17	63
	30 minutes	150	15 6	23	59
	1 hour	190	21 0	25	54
	2 hours	145	15 6	24	60
	3 hours	110	0	17	60
14	Fasting	95	0	28	60
	30 minutes	115	0	29	61
	1 hour	85	0	24	62
	2 hours	85	0	24	61
	3 hours				63
15	Fasting	100	0	10	65
	30 minutes	175	15 6	15	59
	1 hour	150	10 4	17	61
	2 hours	95	10 4	11	62
	3 hours	65	0	9	65
16	Fasting	100	0	11	61
	30 minutes	120	5 2	12	59
	1 hour	155	10 4	17	56
	2 hours	130	5 2	11	60
	3 hours	95	0	10	61

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TABLE 8

Glycerine tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO_2 combining power
		mgm per cent	*mgm per cent*	*volumes per cent*
31	Fasting	90	10	57
	30 minutes	95	10	57
	1 hour	95	15	61
	2 hours	95	12	58
	3 hours	95	10	58
32	Fasting	90	14	62
	30 minutes	105	14	61
	1 hour	110	12	62
	2 hours	110	12	62
	3 hours	100	(Lost)	61
33	Fasting	85	12	67
	30 minutes	80	14	69
	1 hour	80	12	70
	2 hours	80	12	68
	3 hours	80	12	68

TABLE 9

Lactic acid tolerance test

Case	Time	Blood glucose	Blood lactic acid	CO_2 combining power
		mgm per cent	*mgm per cent*	*volumes per cent*
34	Fasting	90	11	63
	30 minutes	90	19	60
	1 hour	95	19	56
	2 hours	100	14 5	61
	3 hours	95	11	61
35	Fasting	95	11	61
	30 minutes	90	19	58
	1 hour	90	17	60
	2 hours	90	14 5	60
	3 hours	90	11	60

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31	Fasting	90	10	57
	30 minutes	95	10	57
	1 hour	95	15	61
	2 hours	95	12	58
	3 hours	95	10	58
32	Fasting	90	14	62
	30 minutes	105	14	61
	1 hour	110	12	62
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DISCUSSION

It will be noted that the results fall into two groups, the first three sugars causing a reduction in CO_2 combining power, the others not Associated with the fall in CO_2 combining power is a definite increase in the blood lactic acid, more marked in the case of dihydroxyacetone than with fructose or cane sugar as would be expected from the relative amounts of reduction of the CO_2 combining power in these cases Moreover, the return to previous values for CO_2 combining power and blood lactic acid runs parallel As in the case of the CO_2 combining power alterations in the blood lactic acid after administration of the other sugars are practically negligible In order to gain some idea of the changes involved two men were given five grams of pure lactic acid dissolved in 250 cubic centimeters of water sweetened with saccharin, and tests similar to the foregoing carried out Table 9 shows the results obtained In this connection it should be pointed out that lactic acid in the body is constantly being burned or reconverted to glucose or glycogen so that the values obtained for blood lactic acid as well as the resultant lowering of CO_2 combining power fall short of measuring the total change taking place Particularly will this be important in the later phases owing to the increased oxygenation consequent upon the hyperventilation (Also since the respiratory muscles work on carbohydrate we must expect a shift of respiratory quotient toward 1 0)

To take one method of calculating the CO_2 eliminated Palmer and Van Slyke (9) have shown that it requires 1 0 gram of $NaHCO_3$ to raise the CO_2 combining power one volume per cent in an individual weighing 38 kilograms Taking the average depression[1] of the CO_2 combining power at the half hour period as amounting to eight volumes per cent in an individual of 70 kilograms, 14 grams of $NaHCO_3$ have been lost, equal to one-sixth of a formula weight or 3,750 cc of CO_2 released Providing this patient were in a basal state, 1 calorie per kilogram hour should approximate his needs, or 35 calories the requirement for the half-hour, or 7,300 cc of oxygen With a true respiratory quotient of 0 80 (it would undoubtedly be higher on ac-

[1] Omitting from the average Case IV which requires one hour to attain this reduction in CO_2 combining power.

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absorbed in the first half hour, the formation of more lactic acid may be expected as this remaining sugar reaches the liver   It is evident from the tables that some lactic acid has disappeared at the end of an hour but a continuance of a high respiratory quotient may depend in part on incomplete re-establishment of acid alkali equilibrium, or combustion of the lactic acid, or many other factors   Should the initial CO_2 released be eliminated over a longer period, as there is good reason to believe possible, there is quite sufficient to maintain high CO_2/O_2 ratios for a considerable period   Attention may be called to the fact that the higher values for these ratios reported have been obtained for a very limited period and calculated on the hour basis, a procedure which examination of the protocols in the preceding paper shows is unsuitable and liable to lead to erroneous conclusions

Turning now to another aspect of these results, we wish to call attention to the remarkable parallelism between the changes in CO_2 combining power and blood lactic acid in these cases with the results of the respiratory examination in man (Mason's) or in normal dogs following the administration of dihydroxyacetone as recorded in the preceding paper   In contrast the fixation of CO_2 and blood lactic acid in man and the slow rise and fall of the CO_2/O_2 ratio after glucose administration to man or animals inspires confidence that such extraneous factors play little, if any, part in the alterations of the respiratory quotient after administration of the normal body sugar

Corresponding to the decreased frequency with which the CO_2/O_2 ratio exceeds 1 0, the results with fructose are somewhat less striking both in the reduction of CO_2 combining power and increase in the lactic acid level (table 2)   With them, however, it is still possible to calculate a CO_2/O_2 ratio well above 1 0   Sucrose also shows a smaller change in the CO_2 combining power and blood lactic acid (table 3) Half the administered carbohydrate was really glucose when it reached the liver and, as shown in table 4, glucose has no effect on either CO_2 combining power or blood lactic acid   Likewise, maltose and lactose and galactose have no influence on these (tables 5, 6 and 7)

It would seem apparent that the extraordinary CO_2/O_2 ratios reported by others (1, 2, 3, 4), as well as ourselves (5), after administration of certain carbohydrates are consequentially related to the production of lactic acid in the body and the blowing off of CO_2 neces-

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Whether it be true or not that it provides the necessary chemical energy for the conversion of the ketoses to glucose, a further implication of the lactic acid production by these sugars occurs to one For some reason lactic acid is produced when the triose or fructose is fed The only source of lactic acid known to occur in the body is glucose or glycogen If it could be produced from triose itself the triose administered intravenously to eviscerated animals would not remain unchanged (9) The process glycogen→lactic acid involves an energy reduction change which must be charged against the foodstuffs initiating the lactic acid production As, according to Meyerhof, this reduction amounts to 0 72 calorie per gram of lactic acid produced, a considerable reduction in the physiological caloric value of the foodstuff is caused directly as well as through the extra work induced by the acid stimulating respiration In our opinion such an action does not enhance the therapeutic value of either sugar in diabetes It is perhaps not a fortuitous circumstance that most of the important carbohydrate used by man and animals is convertible directly to glucose before absorption

SUMMARY AND CONCLUSIONS

The results of the examination of the carbon dioxide combining power and blood lactic acid after the administration of certain carbohydrates have been tabulated and discussed Certain sugars—dihydroxyacetone, fructose and cane sugar—cause a lowering of the carbon dioxide combining power and a rise in the blood lactic acid, while glucose, maltose, lactose, galactose and glycerine do not These changes take place at the proper time to cause stimulation of respiration and the increased elimination of carbon dioxide noted when such substances are fed and explain the extraordinarily high CO_2/O_2 ratios found We would conclude that such ratios cannot be used as an index of food transformation, combustion or storage of the first substances mentioned There appears no reason to believe that these factors interfere in the use of the ratios as respiratory quotients in the case of the other sugars examined In view of the additional energy

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They (the cincophen derivatives) are chemically related to salicyl and their structure indicates the presence of the quinoline ring which acts as an antipyretic Obviously, important factors with all the compounds are general solubility and absorbability The poor solubility and absorbability probably explain the innocuousness of neocincophen Finally, the combined use of morphine and quinine, both of which are chemically different from all the drugs thus far mentioned but which are nevertheless therapeutically efficient in rheumatic fever, indicates the relative unimportance of chemical composition and structure of these therapeutic drugs and of the specificity of salicyl in this disease The speculations on the chemical side of the question have not led to anything definite pertaining to the mechanism of anti-rheumatic action

Since this review Masters (5) has shown that sodium salicylate has no effect on the normal human electrocardiogram and therefore does not account for any of the electrocardiographic changes noted in rheumatic fever Furthermore, Levy and Turner (6) have shown that following salicylate therapy, in addition to the usual anti-symptomatic effect, there was a gradual reduction of the P-R interval to within normal limits in patients with rheumatic heart disease On withdrawing the drug a prolongation of the conduction time recurred We know of no such studies with tolysin

Because we had under observation carefully controlled cases of juvenile rheumatic fever with no arthritis but with an active infection evidenced by fever, loss of weight and leucocytosis, we were interested in observing the action of tolysin on this phase of the disease

METHODS

In selecting the cases it was necessary to know that an active infection was present and demonstrable, and careful allowance was made for the natural course of the disease It is well known that the acute forms may subside more or less completely regardless of treatment although subject to recurrences over a period of years Chronic rheumatic carditis manifests too few signs of infection to be good material for study We have, therefore, selected six carefully controlled cases from the Children's Heart Hospital of Philadelphia all of the subacute type In these, three well-recognized criteria of infection were present, viz fever, leucocytosis and loss of weight, all of which had been stationary for several months previous to treatment It is to be noted that during treatment none of these cases had arthritis or chorea, but that all had definite active cardiac lesions

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The administration of the drug was oral and the dosage is shown in the table This has exceeded in our children the efficient therapeutic dose recognized for adults by Hanzlik (1)

TREATMENT AND RESULTS

Six children with rheumatic heart disease were treated with tolysin and the results are shown in table 1 The diagnosis in all these cases was rheumatic heart disease (active) with mitral stenosis and insufficiency, and enlargement of the heart There were no arrhythmias and although the lesions were fairly severe, none of these patients showed failure of compensation The pulse rate was not affected by treatment in any of these patients

The absence of any demonstrable effect of tolysin upon the weight, temperature and leucocytosis in this type of rheumatic heart disease is evident from the above data

Toxicity

Toxic symptoms of the drug were not found, although sought for in every case Two children each vomited once during the course of treatment but as they were not sick before or after the vomited dose, and as the trouble was very obviously due to the mechanical difficulty of children swallowing pills, the form of administration and not the action of the drug was blamed for this None of the cases showed tinnitus aurium, or other toxic effects and from clinical observations we agree with Barbour and Lozinsky (7) that tolysin is non-toxic

Comment

It is evident that such cases are a very severe test of any drug therapy The low grade fever of chronic tuberculosis would perhaps be a comparable condition

The failure of tolysin to act on this condition is presumably due to the fact that these patients with very low temperatures are not suitable subjects for its antipyretic effects Hanzlik (1) makes it quite clear that whatever action these drugs may have on arthritis or carditis, the results are almost entirely accounted for by antipyresis and analgesia In Miller and Boots (3) cardiac series where the fever was

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condition of the kidneys in cardiac patients after having returned to a state of compensation and in doing so have correlated the tests which are most frequently used

In patients recently recovered from attacks of heart failure, tests were made a few days before sitting up The patients were taking ward diet, free of salt except that used in cooking The tests selected were (1) the urea concentration index (the Van Slyke index) described by Van Slyke, Linder, Hiller, Leiter and McIntosh (1926), (2) the phenolsulphonephthalein test, (3) the concentration test, and (4) the dilution or water test

1 The significance of ascertaining the concentrating power of the kidneys for urea under standard conditions is stated by McIntosh and Reimann (1926) to be "The significance of the urea concentration index may be described by stating that it represents the number of times the kidneys concentrate urea in excreting it from the blood into the urine, when the urine volume output is at the average normal rate of 1 cc per minute or 1 cc per hour per kilo body weight" The index may also be regarded as representing the number of cubic centimeters of blood cleared of urea by the kidneys when urine is being excreted at the rate of 1 cubic centimeter per minute Values of 35 to 80 for the index are regarded as normal

2 Phenolsulphonephthalein 1 cc was injected intravenously Urine specimens were collected at the end of 1 and of 2 hours The amount of the dye excreted was then estimated The dye was given at the end of the urea concentration test Excretion of 55 per cent or more of the dye in 2 hours was considered to be normal

3 The aim of the concentration test is to study the behavior of the kidneys under mild stress In 1914 Hedinger and Schlayer (1914) introduced a test diet for cases of nephritis which was further elaborated by Mosenthal (1915) in 1915 The test as we have used it was devised in this hospital by Lundsgaard The patients are given 3 dry meals Each meal consists of bread (toasted) 65 grams, butter 15 grams, eggs (scrambled) 100 grams, cream cheese 25 grams, and jam or jelly 15 grams to 20 grams The caloric value of this meal is 600 calories, a total of 1800 calories No water is given from midnight of the day preceding the test until its end On the morning of the test the patient voids at 6 a m This specimen is discarded He voids again at 7 a m , this specimen being saved The dry meals are given at 7 30, 10 00 and 11 40 a m The patient voids at 9 and at 11 a m , at 1 and at 3 p m , each specimen is saved separately The test ends after the specimen is collected at 3 p m The amount and specific gravity of each specimen are estimated In normal individuals the specific gravity rises to 1 030 during this test We have however arbitrarily decided to regard 1 025 to 1 030 as within the normal limits for the purposes of this study

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TABLE 1

Summary of data on compensated cardiac patients

Case number Sex†	Hospital number	Age	Cardiac diagnosis* Etiological	Anatomical	Physiological	Blood pressure	Attacks of heart failure First	Last	Number	Type of failure	Renal function Concentration test. Highest specific gravity	Dilution test Amount	Lowest specific gravity	Urea index	Phenolsulphonephthalein excretion	Blood urea nitrogen	Subsequent history Condition	Years after last tests
		yrs					*years ago*	*years ago*				*cc*			*per cent*	*gms per liter*		
1 (M)	5269	54	Hypertension	Slight enlargement of heart	N R.	$\frac{164}{98} \rightarrow \frac{140}{80}$	0	0	0	Palpitation	1 025	705	1 005	30 0	88 3	0 181	Well	$3\frac{1}{4}$
2 (M) (1)	4631	50	Hypertension	Cardiac hypertrophy dilatation of aorta V.P L.	N R., V P C	$\frac{228}{115}$	0	0	0	Fatigue				44 0	68 0	0 176		
(2)	4842	51	Hypertension	Cardiac hypertrophy dilatation of aorta, V P.L.	N R., V P C	$\frac{210}{120}$	0	0	0	Fatigue				51 0		0 151	Well	$4\frac{7}{12}$
3 (M)	4823	66	Arteriosclerosis	Cardiac hypertrophy mitral insufficiency V P.L	A.F	$\frac{140}{80} \rightarrow \frac{100}{60}$	Present	Present	1	Edema pulmonary congestion				54 2	-	0 177	Died§	During the admission
4 (M)	5001	72	Arteriosclerosis	Cardiac hypertrophy mitral insufficiency chronic myocarditis, V P.L.	A.F	$\frac{100\text{–}120}{60-90}$	4	Present	2	Edema, ascites, hydrothorax	1 024	851	1 005	59 0	61 9	0 179	Well	$4\frac{1}{2}$
5 (F) (1)	4941	53	Hypertension	V.P L	N R.	$\frac{160}{85} \rightarrow \frac{120}{65}$	0	0	0	Fatigue	1 025	615	1 006	66 0	76 0	0 127		
(2)	4996	53	Hypertension	V P L.	N R.	$\frac{110\text{–}130}{65-82}$	0	0	0	Fatigue	1 028	733	1 007	120 0	78 4	0 172		

TABLE 1

Summary of data on compensated cardiac patients

Case number Sex†	Hospital number	Age	Cardiac diagnosis*: Etiological	Cardiac diagnosis*: Anatomical	Cardiac diagnosis*: Physiological	Blood pressure	Attacks of heart failure: First	Attacks of heart failure: Last	Attacks of heart failure: Number	Type of failure	Renal function: Concentration test, Highest specific gravity	Renal function: Dilution test: Amount	Renal function: Dilution test: Lowest specific gravity	Renal function: Urea index	Renal function: Phenolsulphonephthalein excretion	Blood urea nitrogen	Subsequent history: Condition	Subsequent history: Years after last tests
		yrs					*years ago*	*years ago*				*cc*			*per cent*	*gms per liter*		
1 (M)	5269	54	Hypertension	Slight enlargement of heart	N R.	$\frac{164}{98} \rightarrow \frac{140}{80}$	0	0	0	Palpitation	1 025	705	1 005	30 0	88 3	0 181	Well	$3\frac{1}{4}$
2 (1) (M)	4631	50	Hypertension	Cardiac hypertrophy dilatation of aorta V.P L.	N R., V P C	$\frac{228}{115}$	0	0	0	Fatigue				44 0	68 0	0 176		
(2)	4842	51	Hypertension	Cardiac hypertrophy dilatation of aorta, V P.L.	N R., V P C	$\frac{210}{120}$	0	0	0	Fatigue				51 0		0 151	Well	$4\frac{7}{12}$
3 (M)	4823	66	Arteriosclerosis	Cardiac hypertrophy mitral insufficiency V P.L	A.F	$\frac{140}{80} \rightarrow \frac{100}{60}$	Present	Present	1	Edema pulmonary congestion				54 2	-	0 177	Died§	During the admission
4 (M)	5001	72	Arteriosclerosis	Cardiac hypertrophy mitral insufficiency chronic myocarditis, V P.L.	A.F	$\frac{100\text{–}120}{60-90}$	4	Present	2	Edema, ascites, hydrothorax	1 024	851	1 005	59 0	61 9	0 179	Well	$4\frac{1}{3}$
5 (1) (F)	4941	53	Hypertension	V.P L	N R.	$\frac{160}{85} \rightarrow \frac{120}{65}$	0	0	0	Fatigue	1 025	615	1 006	66 0	76 0	0 127		
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TABLE 1—*Continued*

Case number Sex†		Hospital number	Age	Cardiac diagnosis* Etiological	Cardiac diagnosis* Anatomical	Cardiac diagnosis* Physiological	Blood pressure	Attacks of heart failure First	Attacks of heart failure Last	Attacks of heart failure Number	Type of failure	Renal function Concentration test Highest specific gravity	Renal function Dilution test Amount	Renal function Dilution test Lowest specific gravity	Renal function Urea index	Renal function Phenolsulphonephthalein excretion	Blood urea nitrogen	Subsequent history Condition	Subsequent history Years after last tests
			yrs					*years ago*	*years ago*				*cc*			*per cent*	*gms per liter*		
13 (M)	(1)	6323	51	Hypertension	Slight cardiac hypertrophy	N R.	$\frac{200}{130}$	0	0	0	Pain of the eyes	1 025	1,465	1 001	47 8	57 1	0 099		
	(2)	6392	51	Hypertension	Slight cardiac hypertrophy	N R.	$\frac{185}{140}$	0	0	0	Pain of the eyes	1 026	1 305	1 005	64 0	62 8	0 103	Well	1/3
14 (M)		5225	65	Arteriosclerosis	Cardiac hypertrophy chronic myocarditis mitral insufficiency, aortic roughening, V.P R.	N R.	$\frac{150}{110} \rightarrow \frac{130}{80}$	Present	Present	1	Edema	1 028	720	1 005	70 3	56 3	0 206	Died	3/4
15 (M)		5285	20	Rheumatism?	Cardiac hypertrophy cardiac dilatation, mitral stenosis, mitral insufficiency, V P R.	N R., S I.	$\frac{100}{60}$	Present	Present	1	Dyspnea	1 035	997	1 001	52 3	67 6	0 138	Died	3½
16 (M)		6183	56	Arteriosclerosis	Cardiac hypertrophy, coronary thrombosis	N R., hypertension	$\frac{170}{110}$	1/4	1/4	1	Pain	1 028	183	1 018	30 7	71 8	0 087	Well	3/5
17 (M)	(1)	5265	18	Acute rheumatic fever at 9 years tonsillitis, chorea	Chronic myocarditis, V P R.	N R A.P C	$\frac{110}{65}$	Present	Present	1	Pain A P C	1 029	830	1 006	106 0	107 4	0 071		
	(2)	5645	19	Acute rheumatic fever at 9 years tonsillitis, chorea	Chronic myocarditis, V P R.	N.R. A.P C	$\frac{105}{65}$	1	Present	2	Pain, A P C	1 037	885	1 001	67 4	84 4	0 157	Well	2

TABLE 1—*Continued*

Case number Sex†		Hospital number	Age	Cardiac diagnosis* Etiological	Cardiac diagnosis* Anatomical	Cardiac diagnosis* Physiological	Blood pressure	Attacks of heart failure First	Attacks of heart failure Last	Attacks of heart failure Number	Type of failure	Renal function: Concentration test Highest specific gravity	Renal function: Dilution test Amount	Renal function: Dilution test Lowest specific gravity	Renal function: Urea index	Renal function: Phenolsulphonephthalein excretion	Blood urea nitrogen	Subsequent history Condition	Subsequent history Years after last tests
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	(2)	6392	51	Hypertension	Slight cardiac hypertrophy	N R.	$\frac{185}{140}$	0	0	0	Pain of the eyes	1 026	1 305	1 005	64 0	62 8	0 103	Well	¼
14 (M)		5225	65	Arteriosclerosis	Cardiac hypertrophy chronic myocarditis mitral insufficiency, aortic roughening, V.P R.	N R.	$\frac{150}{110} \rightarrow \frac{130}{80}$	Present	Present	1	Edema	1 028	720	1 005	70 3	56 3	0 206	Died	½
15 (M)		5285	20	Rheumatism?	Cardiac hypertrophy cardiac dilatation, mitral stenosis, mitral insufficiency, V P R.	N R., S I.	$\frac{100}{60}$	Present	Present	1	Dyspnea	1 035	997	1 001	52 3	67 6	0 138	Died	3¼
16 (M)		6183	56	Arteriosclerosis	Cardiac hypertrophy, coronary thrombosis	N R., hypertension	$\frac{170}{110}$	¼	¼	1	Pain	1 028	183	1 018	30 7	71 8	0 087	Well	¾
17 (M)	(1)	5265	18	Acute rheumatic fever at 9 years tonsillitis, chorea	Chronic myocarditis, V P R.	N R A.P C	$\frac{110}{65}$	Present	Present	1	Pain A P C	1 029	830	1 006	106 0	107 4	0 071		
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24 (M)	5584	54	Arteriosclerosis	Cardiac hypertrophy chronic myocarditis mitral insufficiency aortic roughening, V P.L.	N R V P C	$\frac{100}{80}$	$\frac{1}{4}$	Present	1	Edema ascites hydrothorax	1 030	94	1 021	34 1	64 4	0 322	Not known	
25 (M)	5204	30	Unknown	Chronic myocarditis, mitral insufficiency	N R.	$\frac{100}{70}$	Present	Present	1	Dyspnea	1 034	899	1 004	90 2	87 5	0 136	Well	$3\frac{1}{4}$
26 (M)	5829	26	Hypertension	Mitral insufficiency	N R	$\frac{160}{80} \rightarrow \frac{130}{65}$	Present	Present	1	Pain	1 026	640	1 003	59 8	70 7	0 130	Well	$1\frac{1}{3}$
27 (M)	5424	52	Unknown	Cardiac hypertrophy chronic myocarditis, mitral insufficiency, V P L	N R	$\frac{125}{90}$	Present	Present	1	Edema hydrothorax	1 025	830	1 001	48 5	67 4	0 142	Died	$\frac{1}{12}$
28 (M)	5401	27	Rheumatism?	Cardiac hypertrophy mitral stenosis mitral insufficiency V P R	A F	$\frac{100}{65}$	6	Present	5	Edema pulmonary congestion, pulmonary hemorrhages	1 031	395	1 003	54 2	93 5	0 189	Died§	$\frac{5}{12}$
29 (F)	6163	61	Arteriosclerosis	Cardiac hypertrophy chronic myocarditis mitral insufficiency	A.F V P C	$\frac{135}{85}$	$\frac{7}{12}$	Present	1	Edema	1 017	385	1 005	42 7	53 3	0 210	Well	$\frac{7}{12}$

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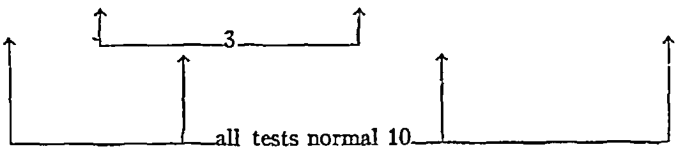
TABLE 2

A summary of results of tests of renal function in cardiac patients

Van Slyke index		Concentration test			Dilution test			Phenolsulphonephthalein test		
Low	Normal	Low	Normal	No data	Low	Normal	No data	Low	Normal	No data
7	28	9	22	4	13	18	4	1	33	1



phenolsulphonephthalein was normal in all except one (case 10) of 35 patients The Van Slyke index was normal in 28 patients (41 tests) (tables 1 and 2), and below normal, though in no instance greatly so, in 7 patients (9 tests) In 10 patients the kidneys failed to concentrate urine to a specific gravity of 1 026 to 1 030, though in only one case did it fall below a specific gravity of 1 020 (case 29, 1 017) In 17 patients the results first obtained by use of the dilution test were abnormal In 7 the only abnormality was failure to excrete 750 cc or more of the 1000 cc of water ingested In 3, although the specific gravity did not fall to 1 005, a normal amount of water was nevertheless excreted In the other 8 patients[1] (that is to say of the 17) the amount excreted was less than 750 cc and beside the specific gravity did not fall to 1 005 Five of the 17 showed abnormalities in the concentration test as well In one patient (case 34) after prolonged rest in bed, when the blood pressure fell, there were decreased values except in the concentration and phenolsulphonephthalein tests After taking a salt free diet for 6 weeks when the blood pressure fell further, the renal function improved, as indicated by the presence of normal dilution although concentration rose only to 1 022 In this patient, the diagnosis is not certain He may have passed through a stage of acute nephritis to which hypertension was secondary and not primary or essential In 10 of the 35 patients the values at one time were normal in all the tests, while in 25 the function was decreased at some time in one or more of the tests

[1] Several patients during several years fall now in one group and now in another due to change in the renal function even according to the same tests

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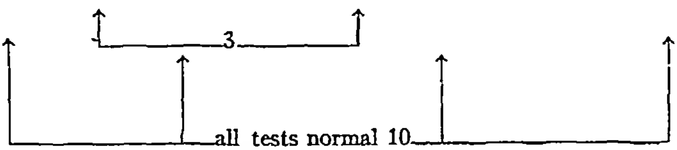

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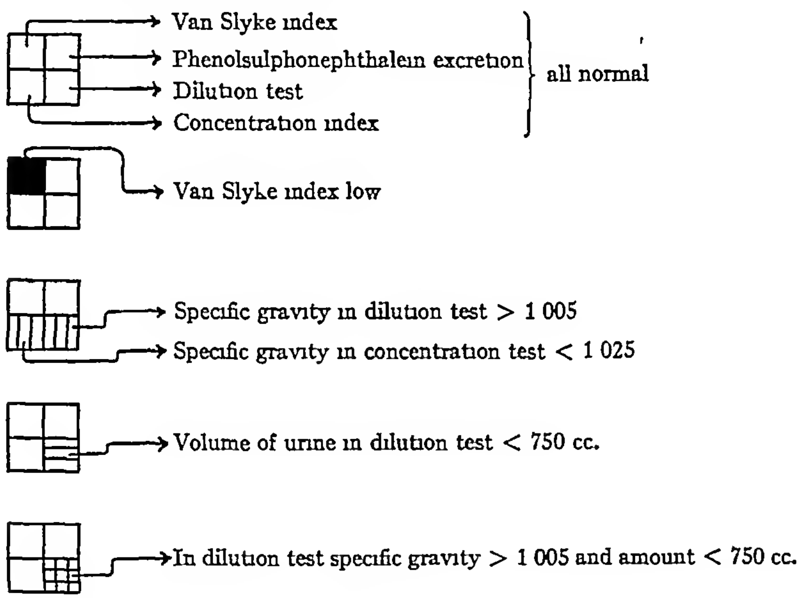
dominated In the fourth group are 3 patients (cases 2, 5 and 9) in whom heart failure manifested itself as *fatigue* In the fifth group is one patient (case 1) who complained only of *palpitation* No special

FIG 1 In this figure the renal functions of patients are charted at the age which they were estimated Each column represents a patient The ordinates represent years of age Symbols indicate renal function, and the etiology of the cardiac disease The years in which infections occurred, cardiac lesions were diagnosed, symptoms first appeared and attacks of heart failure occurred are also indicated



● = Attack of acute rheumatic fever
\+ = Attack of chorea
← = Occurrence of symptoms or of cardiac failure
⧧ = Cardiac lesion diagnosed
□ = Etiology is *acute rheumatic fever*
■ = Etiology is *unknown*
△ = Etiology is *hypertension*
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complaints were to be elicited from 2 patients (cases 13 and 34) who were the subjects of hypertension Many of the impairments in renal function were discovered in the patients subject to attacks of *con-*

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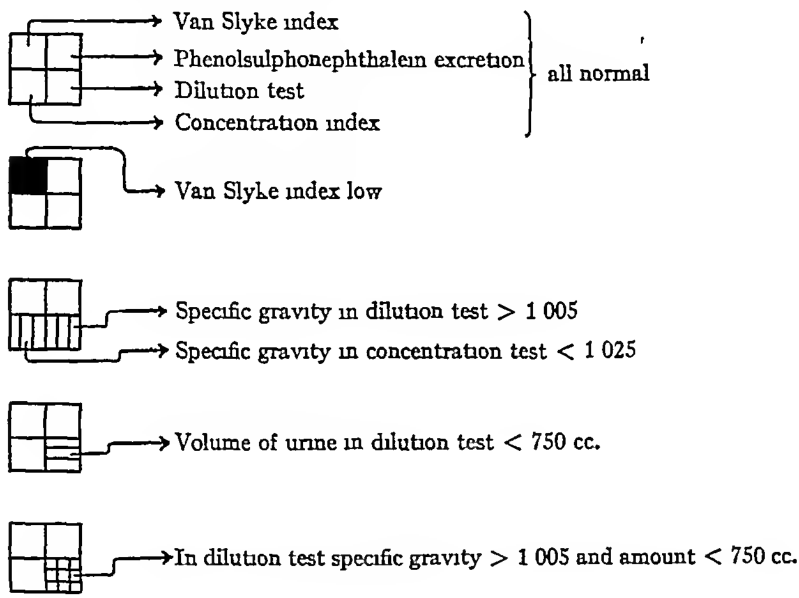

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years to one month in 35 patients Impairment of function did not appear to vary with the duration of the disease, whether months or years Impairments occurred about as frequently in those who had had only one, as in those who had had repeated attacks The degree of impairment in short did not parallel the number of attacks of heart failure (see discussion) Nor did there appear to be an outspoken relation between the duration of heart disease[3] and the degree of impairment, so far as the concentrating and diluting functions of the kidneys are concerned

Correlation of age and renal function in patients with heart disease There are 50 observations in 38 patients (Figure 1) Twelve (cases 8, 12, 15, 17, 19, 22, 25, 26, 28, 31, 34, and 35) range in age between 15 and 30 years In seven (cases 8, 12, 15, 17, 19, 28 and 31) of these, or about 60 per cent, the function appeared normal in all the tests But in 23 patients ranging in age between 38 and 72 years, this was true in 3 only (cases 5, 13 and 27) Although the number of cases is too few for statistical statement, impairments in renal function are certainly more frequent in heart patients in the decades after 30 years

Blood urea in heart disease The blood urea was below 0 200 gram per liter in all except 3 patients

DISCUSSION

We have found, on the whole, little impairment in those renal functions which we have been able to measure in patients suffering from chronic heart disease The number studied is of course small for statistical treatment The Van Slyke index was abnormal in only 8 patients and phenolsulphonephthalein excretion was diminished in only one The most frequent impairment was the diluting ability of the kidneys, the concentrating function was second This was the situation during the stage of compensation Little or no permanent damage to the kidneys need become established for many years During the stage of congestion renal function as measured by the Van Slyke index, the phenolsulphonephthalein excretion, and the Mosenthal test diet, is however greatly diminished Afterwards some impairment becomes evident

[3] The duration of heart disease dates from the time when a diagnosis of heart disease was made, it need not of course coincide with the date of the first attack of heart failure

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sis and insufficiency of rheumatic origin In the *first* (case 12) all the tests for renal function were normal after recovery from a third attack of heart failure One year later, after recovery from a fourth attack, he was no longer able to excrete urine of low specific gravity The amount also descreased as was seen in the dilution test After the eighth attack two years later, both functions, concentrating as well as diluting, were abnormal While damage to the heart was progressing continuously change in kidney function also occurred The general condition and the behavior of the kidneys took a parallel downward course The *second* patient (case 19) likewise exhibited normal renal functions after recovery from a first attack of heart failure Three years later, after the third attack, he could no longer excrete the normal amount of water in the dilution test, nor could he lower the specific gravity to 1 005 His capacity for exertion had meanwhile diminished The *third* patient (case 22) had suffered from heart disease for 14 years and had suffered from 6 attacks of heart failure when the first observations were made These revealed abnormality in the concentration test One year later, after the seventh attack, the dilution as well as the concentration test was abnormal During this time he failed rapidly

Three patients (cases 5, 17, and 23, fig 1) showed progressive improvement in renal function over a period of several years, clinical improvement occurred at the same time A fourth patient (case 6) remained unchanged over a period of 5 years, both from the point of view of the clinical course and of the kidneys

Our observations as we have said, include however neither a sufficiently large number of patients nor do they cover sufficiently long periods to warrant our drawing conclusions on the meaning of the tests we have used from the point of view of prognosis The situation is in fact confusing Some patients are alive and are carrying on work without signs of heart failure, though their renal functions are as greatly diminished as were those in others shortly before death

Deterioration in the renal functions was most common in the arteriosclerotic and hypertensive groups in which they were normal in only two individuals (cases 5 and 13), less common in the acute rheumatic group in which were most of the patients with normal function Beyond the age of 30 normal function was present in only three (cases 5, 13 and 27) The lower age may be 40 or 50 years if larger numbers

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4 In 17 patients, that is to say in one half the patients studied, the dilution test revealed abnormality either in the ability to excrete the normal amount of water or in the failure of the specific gravity to fall or in both

5 The concentration test showed impairment in 10 patients

6 Diminished renal function was found in all except 3 patients who were more than 30 years of age

7 A correlation exists between arterio-sclerosis and hypertension and decrease in renal function

8 The impairments of renal function were found more frequently in patients who suffered from congestive heart failure

9 There was no correlation between duration of heart disease and impairment in renal function

CONCLUSIONS

Although the number of patients is too small to make statistical inferences, the following facts emerge from analysis of the data

1 After 30 years of age, normal renal function is found rarely in patients with cardiac disease

2 Normal function is rare in patients with circulatory disease of arterio-sclerotic or hypertensive etiology

2a Conclusions 1 and 2 are correlated, since arterio-sclerosis and hypertension are diseases of the later decades

3 Impairments of renal function were found most frequently in patients subject to repeated attacks of congestive heart failure

4 Although correct in general, conclusion 3 requires modification by the statement that the degree of impairment did not parallel the number of attacks of failure

4a During intervals between attacks of heart failure there may be no impairment of renal function

5 There was no correlation between the duration of heart disease and the degree of impairment

5a There was no correlation between the length of time since the onset of the first attack of heart failure and the degree of impairment

6a The Van Slyke index of urea excretion and the phenolsulphonephthalein excretion are usually normal

4 In 17 patients, that is to say in one half the patients studied, the dilution test revealed abnormality either in the ability to excrete the normal amount of water or in the failure of the specific gravity to fall or in both

5 The concentration test showed impairment in 10 patients

6 Diminished renal function was found in all except 3 patients who were more than 30 years of age

7 A correlation exists between arterio-sclerosis and hypertension and decrease in renal function

8 The impairments of renal function were found more frequently in patients who suffered from congestive heart failure

9 There was no correlation between duration of heart disease and impairment in renal function

CONCLUSIONS

Although the number of patients is too small to make statistical inferences, the following facts emerge from analysis of the data

1 After 30 years of age, normal renal function is found rarely in patients with cardiac disease

2 Normal function is rare in patients with circulatory disease of arterio-sclerotic or hypertensive etiology

2a Conclusions 1 and 2 are correlated, since arterio-sclerosis and hypertension are diseases of the later decades

3 Impairments of renal function were found most frequently in patients subject to repeated attacks of congestive heart failure

4 Although correct in general, conclusion 3 requires modification by the statement that the degree of impairment did not parallel the number of attacks of failure

4a During intervals between attacks of heart failure there may be no impairment of renal function

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Case 20 *The anatomical diagnosis* was calcification of the aortic valves, stenosis of the aortic valves, cardiac hypertrophy, advanced atherosclerosis of the aorta, moderate atheromatosis of the aortic cusp of the mitral valve and of the coronary vessels, arteriosclerosis of the kidneys, infarcts of the kidneys, cyanotic induration of the liver, passive congestion of the spleen and kidneys, ascites, edema of the legs and intestines, serous pericarditis, sero-fibrinous pleurisy of the left pleural cavity, localized pleural effusion in a space between the upper and middle lobes of the right lung, osteoporosis of the sternum *The microscopical diagnosis* was calcification of the aortic valves, chronic endocarditis and pericarditis of the left auricle, atheromatosis of the aortic cusp of the mitral valve, calcifying atherosclerosis of the intima of the thoracic part and of the intima and media of the abdominal part of the aorta, calcifying atherosclerosis of the splenic artery, adhesive pleurisy of the right pleural cavity, purulo-fibrinous pleurisy in the space between the upper and middle lobes of the right lung, chronic passive congestion of the lungs, atrophic induration of the liver, chronic passive congestion of the liver, *atherosclerosis and passive congestion of the kidneys, renal infarction*, passive congestion of the spleen and adrenal glands

Case 21 *The anatomical diagnosis* was extreme thrombosis and atherosclerosis of the left coronary artery, focal thrombosis and atherosclerosis of the right coronary artery, myocardial degeneration, healed and recent myocardial infarcts, adherent pericardium, fibrous pleurisy, anthracosis, emphysema, general arteriosclerosis, venous stasis of the liver, perisplenitis, perihepatitis, abdominal adhesions, hyperplasia of the spleen, arteriosclerosis of the kidneys, infarcts of the kidneys *The microscopical diagnosis* was healed canalized thrombi and recent thrombosis of the coronary arteries, endocardial thickening, fibrosis and recent infarction of the left ventricle, atherosclerosis of the aorta, cyanotic atrophy of the liver, fibrous thickening of the pleura, anthracosis, perisplenitis, *infarction of the kidneys, atherosclerosis of the kidneys*

Case 28 *The anatomical diagnosis* was cardiac hypertrophy, chronic cardiac valvular disease (mitral and aortic), pericarditis, broncho-pneumonia, venous stasis of the organs *The microscopical diagnosis* was chronic endocarditis, anemic infarcts of the heart, chronic passive congestion of the liver, passive congestion of the spleen, *passive congestion of the kidneys*, congestion and edema of the adrenal glands, normal aorta

Case 32[4] *The anatomical diagnosis* was chronic endocarditis, mitral stenosis and aortic stenosis, cardiac hypertrophy and dilatation, sclerosis of the pulmonary artery, atelectasis of the lower and middle lobes of the right lung, healed bilateral apical tuberculosis, *chronic passive congestion of* the liver, spleen and *kidneys, healed infarcts of* the spleen and *kidneys*

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The statistics of the Thyroid Clinic of the Massachusetts General Hospital indicate that following either x-ray treatment or subtotal thyroidectomy, *permanent* myxedema is a rare occurrence A subtotal thyroidectomy in this hospital involves the removal of at least three-fourths and usually five-sixths to seven-eights of the gland Iodine has been used for several months post-operatively in many of the cases since the year 1924 The type of x-ray therapy used in the majority of instances was the exposure of both thyroid and thymus glands to about two-thirds the erythema dose Treatments were usually given 3 to 4 weeks apart During the period 1915–1926 inclusive, 465 cases of toxic goiter (for the most part exophthalmic goiter) were treated as follows

130 by x-ray only
213 by subtotal thyroidectomy only, in one or more stages
122 by more limited operations, often with x-ray in addition, or else by subtotal thyroidectomy and x-ray combined

Only 8 cases of myxedema which was apparently permanent were observed among the above 465 cases, i e , about 2 per cent Five of these occurred after x-ray treatment, 1 after subtotal thyroidectomy,

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TABLE 1

Skeleton outlines of clinical and basal metabolic histories on the four uncharted cases of permanent myxedema following treatment for thyrotoxicosis

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
			per cent		*kgm*		
6	Mr B S	October 12, 1915	+78	103	50 0		Exophthalmic goiter of 2 years' duration
	Lab No 33						
	Age 24	October 13, 1915				*First x-ray Treatment*	
		June 5, 1916	+51	96	52 7		Improved
		July 5, 1916				*Sixth x ray treatment*	
		February 1, 1917	+1	73	60 0		Well
		April, 1919					Well
		May 5, 1919	−14	56	59 0		Well No myxedema
		September, 1920					Onset of symptoms of myxedema
		May 16, 1921	−20	52	61 0	Thyroid extract, grs *IVss* daily	*Myxedema*
		June 1, 1921	−8	60	58 5		Much improved
		June 13, 1921	−13	52	58 0	Thyroid increased to grs *VIss* daily	
		September 19, 1921	−1	54	57 5		Well
		March 20, 1922				Thyroid omitted	
		March 30, 1922	−15	49	56 5	Thyroid extract, grs *IVss* daily	
		About October 1, 1922				Thyroid omitted	
		October 12, 1922				Thyroid extract, grs *IIIss* daily	*Recurrence of myxedema*
		June 21, 1923	+9	60	56 0		No myxedema
		February 2, 1925	+2	56	56 9		No myxedema

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TABLE 1—*Continued*

Case number	Description	Date	Basal metabolic rate	Pulse	Weight	Treatment	Clinical notes
			per cent		*kgm*		
8	Mrs D N Lab No 40 Age 27	November 9, 1915	+28	103	55 8	Diet and rest	Exophthalmic goiter of 18 months' duration
		February 20, 1923	+44	132	53 0		Persistent thyrotoxicosis Hemophilia Late syphilis
		April 15, 1923	+34	*110*			
		April 30, 1923				*First x-ray treatment*	
		September 10, 1924	+30	94	64 0		Some improvement
		September 25, 1924				*Third x-ray treatment*	Myocardial failure
		September 26, 1924				Lugol's solution	
		September 30, 1924	+16	62	63 0		
		October 8, 1924				*Subtotal thyroidectomy*	
		October 15, 1924				Lugol's omitted	
		November 26, 1924	−6	80	61 0		Well since operation
		September 2, 1925					No thyrotoxicosis
		September 12, 1925				X-ray treatment of spleen	Secondary anemia Menorrhagia
		October 14, 1925	−5	84	61 5		Well
		January 4, 1926 to January 20, 1926				X-ray treatment of pelvis	Menorrhagia
		April 21, 1926					Well except for headaches No catamenia since January, 1926
		June 5, 1926	−12	78	63 9	Lugol's solution	*Myxedema*
		June 21, 1926	−25	68	64 8		
		June 25, 1926				Lugol's omitted Thyroid extract (Armour's) grs *IVss* daily	

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The diagnosis of myxedema was definite in all the cases except no 8 (table 1) She had no noticeable edema, but her subjective symptoms

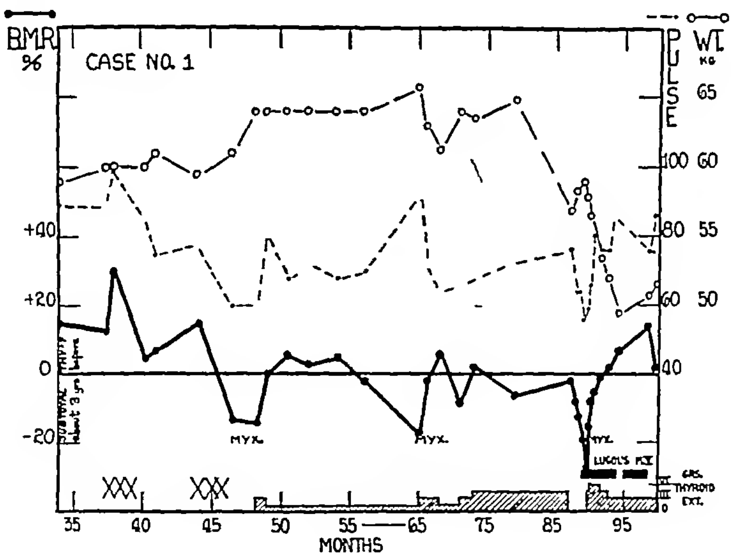

Fig 1 Lab No 1505 Miss F F T Age 47 Permanent Myxedema Occurring within 3 Months after X-Ray Therapy (X) Preceded by Subtotal Thyroidectomy (about 3 Years before First Metabolism Determination) for Exophthalmic Goiter

Marked exophthalmos persists to date Maintenance dose of thyroid extract is 3 grains daily In this and subsequent charts, black areas denote Lugol's medication, and cross-hatched areas, thyroid medication

were characteristic and disappeared on thyroid therapy Case 2 (fig 2)[6] is typical of the group, and, when myxedematous, presented the following signs and symptoms

She was dopey, lacked energy, had a poor appetite, fatigued very easily and felt cold all the time She had dyspnea on exertion Her speech was slow and thick

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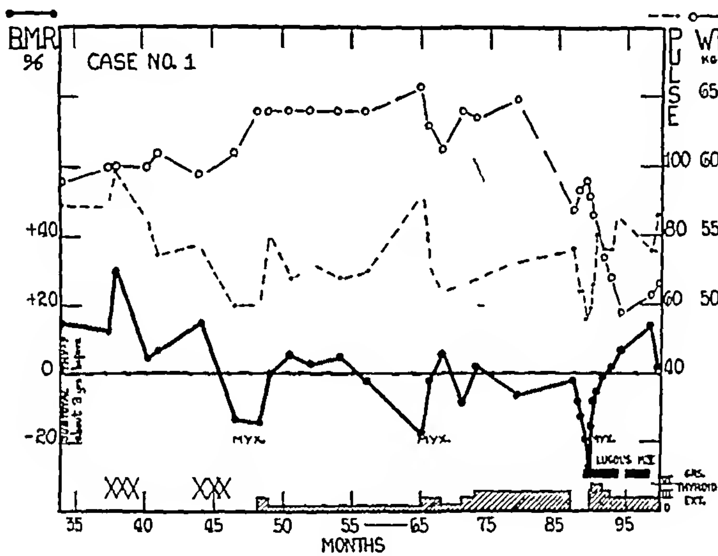

FIG 1 LAB NO 1505 MISS F F T AGE 47 PERMANENT MYXEDEMA OCCURRING WITHIN 3 MONTHS AFTER X-RAY THERAPY (*X*) PRECEDED BY SUBTOTAL THYROIDECTOMY (ABOUT 3 YEARS BEFORE FIRST METABOLISM DETERMINATION) FOR EXOPHTHALMIC GOITER

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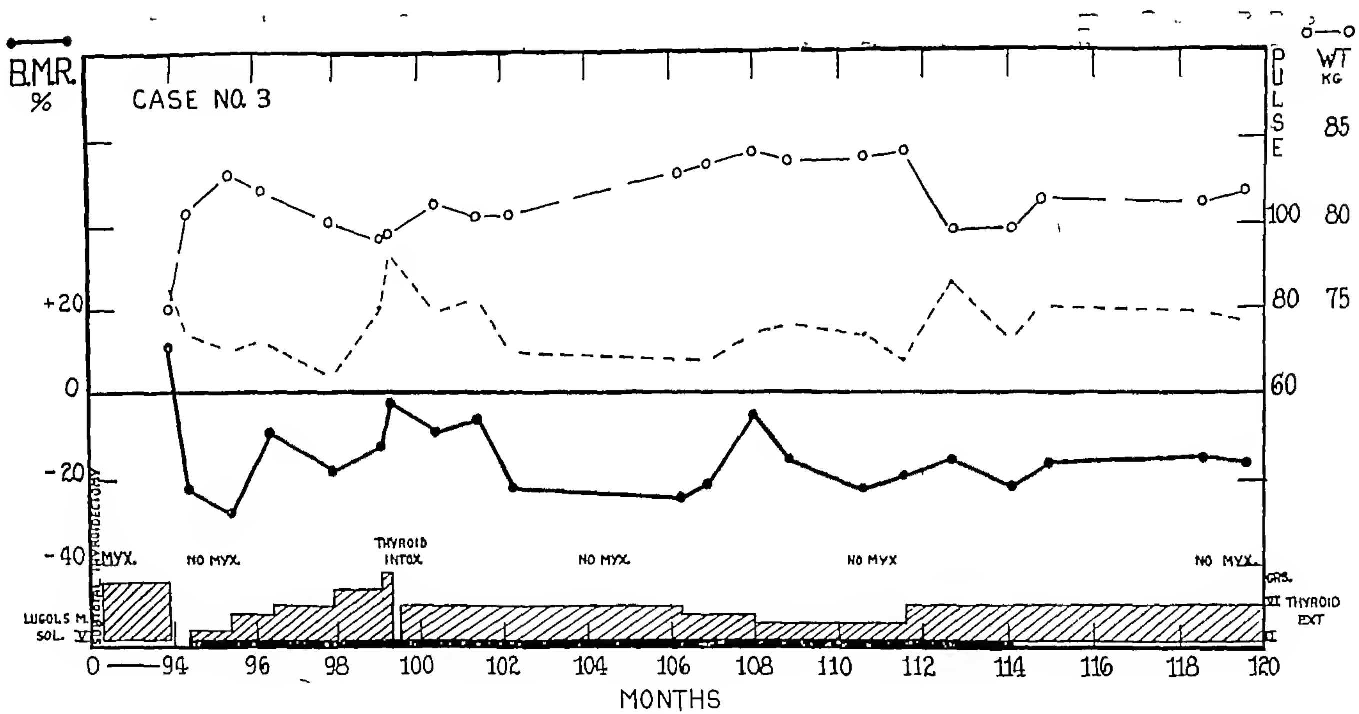
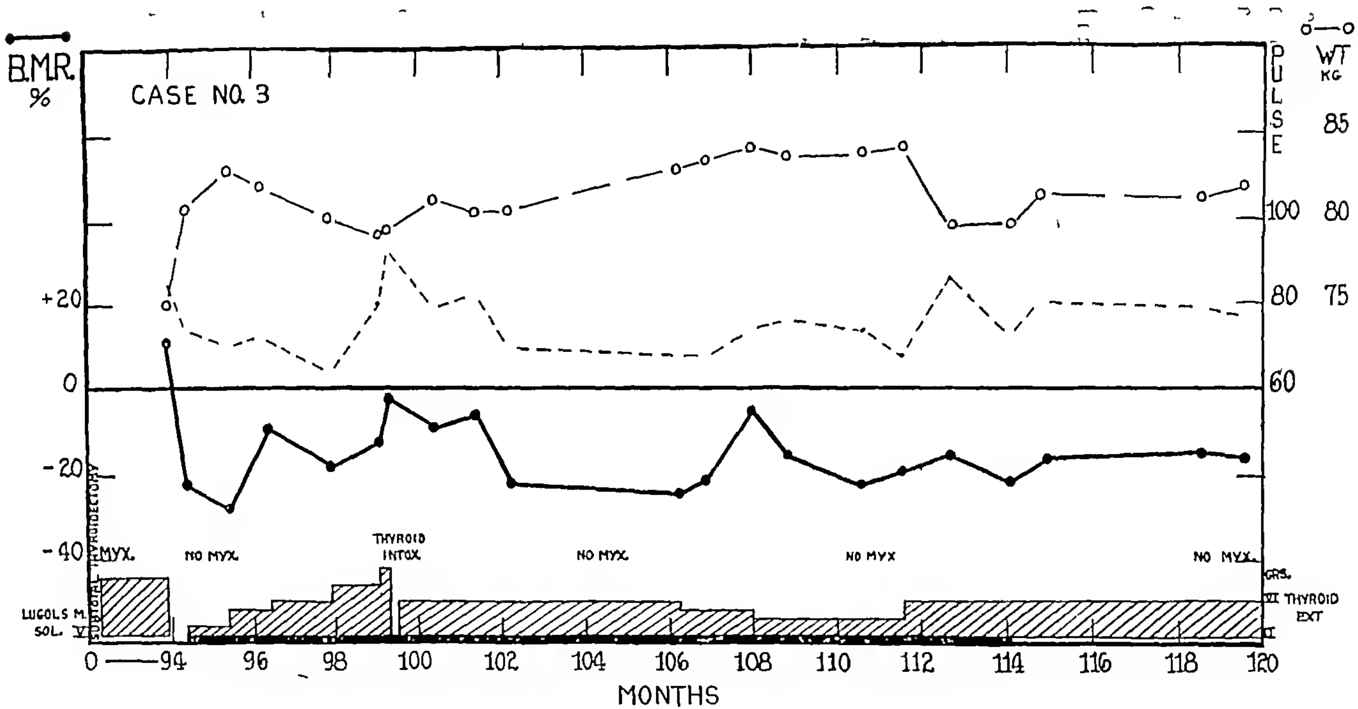


FIG 3 LAB NO 3947 MR R C P AGE 49 COMBINED MYXEDEMA AND NORMAL LOW BASAL METABOLIC RATE FOLLOWING SUBTOTAL THYOIDECTOMY FOR EXOPHTHALMIC GOITER

The myxedema occurred within 6 months after the thyroidectomy The patient's metabolism remained low in spite of 6 grains of thyroid extract (*BW*) daily, but there were no symptoms of myxedema Raising his metabolism to standard normal by a dose of 12 grains daily produced thyroid intoxication



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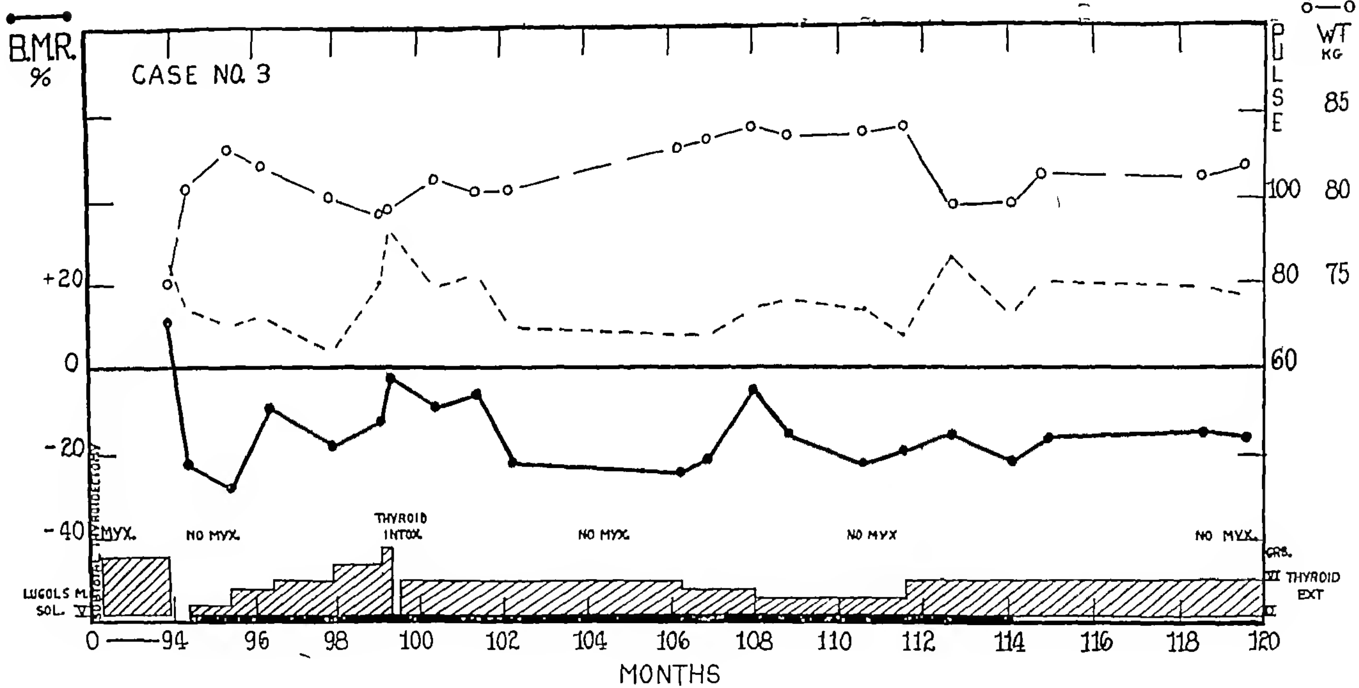

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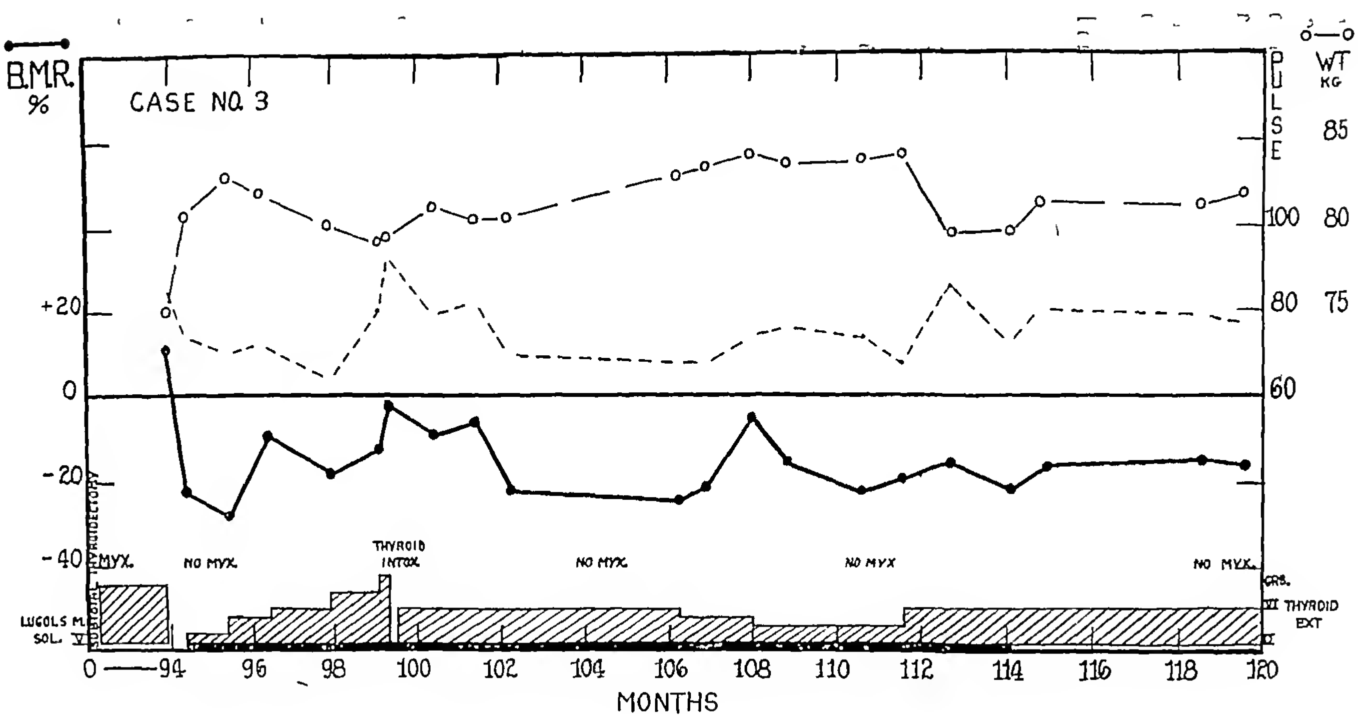

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One of the most striking features brought out by a study of these cases was the late onset of the myxedema after x-ray therapy for thyrotoxicosis This has been previously noted by Means and Holmes

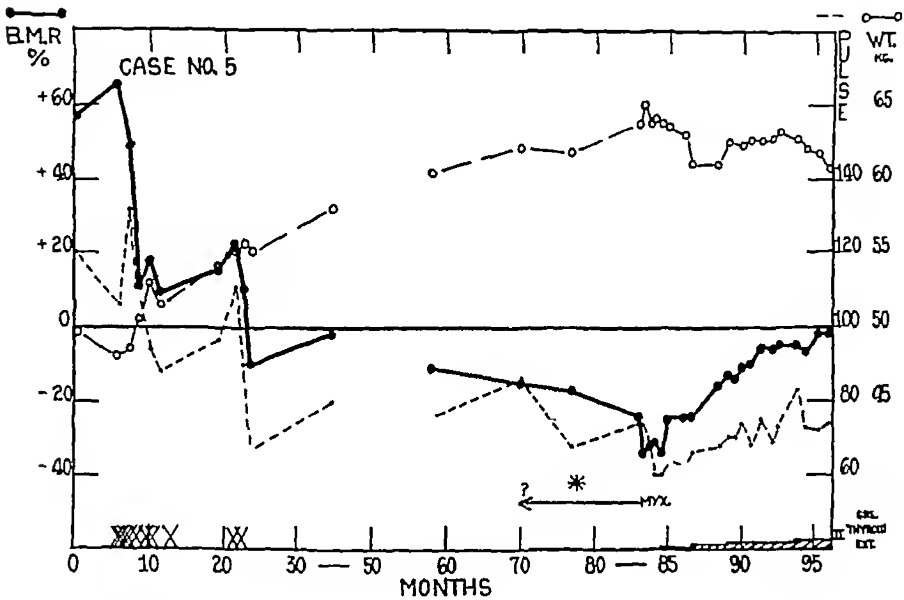

FIG 5 LAB NO 628 MRS M J AGE 41 ONSET OF MYXEDEMA 3 TO 5 YEARS AFTER X-RAY THERAPY (X) FOR TOXIC GOITER

Symptoms noted shortly before radiation and removal of left breast for carcinoma (*) The patient is well and has a standard normal metabolic rate on 1½ grains of thyroid extract daily

(8) in two patients In the 5 cases thus treated, the times of onset were as follows

Case	*Years after last x-ray treatment*
2 (fig 2)	4 to 5
4 (fig 4)	5 to 8
5 (fig 5)	3 to 5
6 (table 1)	4
7 (table 1)	2 to 6

(In this connection, it is of interest that the onset of myxedema in the case of temporary myxedema following x-ray therapy was also late,

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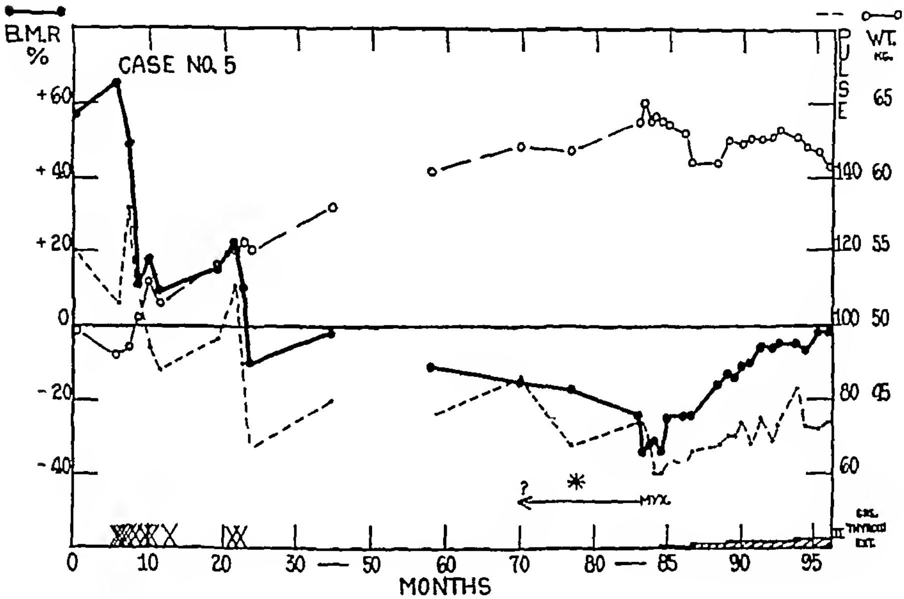

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When next seen in this hospital in June, 1909, she was taking thyroid, but irregularly. Her goiter and exophthalmos had disappeared. She had no edema, her speech was normal and her facial expression "only suggestive, but not characteristic of myxedema." Her tongue was large, her hair and skin were dry and she felt chilly. She began taking thyroid regularly and felt better. In December, 1910, it was regulated at 5 grains (Burroughs Wellcome) daily.

In the next nine years, she underwent four operations in other hospitals, two for removal of Fallopian tubes, ovaries and uterus on account of menorrhagia, and two for herniae in the scars. During this time, whenever thyroid extract was omitted she became myxedematous again. In January, 1920, at the time of her last operation, a high blood pressure was noted. Her dose of thyroid varied from 2 to 4 grains daily for some time thereafter. In April, 1926, she was in another hospital because of a recurrence of her myxedema. She had her first basal metabolism determination, which was minus 28 per cent. She was discharged improved on 3 grains of thyroid extract daily.

In September, 1926, she returned to this hospital because of failing vision. She stated that she was taking 8 grains of thyroid (unknown brand) daily, but this was doubtful in view of her symptoms. She looked myxedematous. Her face was puffy. She was lethargic and always tired and sleepy. Her voice was hoarse, her tongue large, her hair coarse and her skin dry. Her heart was enlarged and her blood vessels somewhat sclerosed. Her blood pressure was $\frac{238}{130}$. Her basal metabolism was plus 3 per cent and her pulse rate 80. Thyroid was omitted until December 1926, during which time her metabolism fell to minus 20 per cent, and her signs and symptoms became so pronounced that there was no doubt about the diagnosis of myxedema. She had the high protein concentration in her spinal fluid and the albuminuria so often present in this disease (9). She improved on gradually increasing doses of Armour's thyroid extract. The albuminuria disappeared and the protein content of the spinal fluid decreased markedly on this medication (9). Four grains daily, however, produced symptoms of thyroid intoxication, viz., nausea, vomiting, precordial and epigastric pain and palpitation. These disappeared when thyroid was omitted for a short time. A dose of 2 grains daily was resumed. This dose proved satisfactory, and maintained her metabolism at a normal level for several months. There were no signs nor symptoms of myxedema, and she felt as well as could be expected in view of her hypertension. After a time, however, she developed marked precordial pain and palpitation with a basal metabolic rate of plus 26 per cent. It was again necessary to stop the administration of thyroid extract. Her myxedema recurred. After an interval of 5 months, 3 grains of Armour's thyroid daily was started, but in a few days caused a recurrence of her precordial pain. The dose was finally regulated at $\frac{1}{2}$ grain of Armour's thyroid daily. This has maintained the basal metabolic rate at a normal level, has caused no precordial pain, and her myxedema has not recurred.

When next seen in this hospital in June, 1909, she was taking thyroid, but irregularly Her goiter and exophthalmos had disappeared She had no edema, her speech was normal and her facial expression "only suggestive, but not characteristic of myxedema." Her tongue was large, her hair and skin were dry and she felt chilly She began taking thyroid regularly and felt better In December, 1910, it was regulated at 5 grains (Burroughs Wellcome) daily

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In September, 1926, she returned to this hospital because of failing vision She stated that she was taking 8 grains of thyroid (unknown brand) daily, but this was doubtful in view of her symptoms She looked myxedematous Her face was puffy She was lethargic and always tired and sleepy Her voice was hoarse, her tongue large, her hair coarse and her skin dry Her heart was enlarged and her blood vessels somewhat sclerosed Her blood pressure was $\frac{238}{130}$ Her basal metabolism was plus 3 per cent and her pulse rate 80 Thyroid was omitted until December 1926, during which time her metabolism fell to minus 20 per cent, and her signs and symptoms became so pronounced that there was no doubt about the diagnosis of myxedema She had the high protein concentration in her spinal fluid and the albuminuria so often present in this disease (9) She improved on gradually increasing doses of Armour's thyroid extract The albuminuria disappeared and the protein content of the spinal fluid decreased markedly on this medication (9) Four grains daily, however, produced symptoms of thyroid intoxication, viz , nausea, vomiting, precordial and epigastric pain and palpitation These disappeared when thyro d was omitted for a short time A dose of 2 grains daily was resumed This dose proved satisfactory, and maintained her metabolism at a normal level for several months There were no signs nor symptoms of myxedema, and she felt as well as could be expected in view of her hypertension After a time, however, she developed marked precordial pain and palpitation with a basal metabolic rate of plus 26 per cent It was again necessary to stop the administration of thyroid extract Her myxedema recurred After an interval of 5 months, 3 grains of Armour's thyroid daily was started, but in a few days caused a recurrence of her precordial pain The dose was finally regulated at ½ grain of Armour's thyroid daily This has maintained the basal metabolic rate at a normal level has caused no precordial pain, and her myxedema has not recurred

basal metabolism in the two cases in which the diagnosis of myxedema appeared to be definite, are given below

Case 11 (fig 6) Lab No 348[9] Mrs M B Age 38 In September, 1920, 8 months after 6 x-ray treatments (ending in January, 1920) for toxic goiter, she was clinically well and had a basal metabolism of minus 3 per cent In February, 1921, her metabolism was still normal, and the only symptom present was numbness of the hands She looked somewhat pale and her skin was a little dry In August, 1921, 1½ years after the x-ray treatment, her metabolic rate was down to minus 35 per cent There had been a weight gain of 9 kgm since 1920 She had not been well for 3 months She complained of numbness of her hands, general weakness, pains in her legs on climbing stairs, and marked constipation She felt cold and did not perspire during the hot days She appeared dull Her face was expressionless, her speech slow and her skin dry and coarse Her lips were bluish and her face and conjunctivae pale A diagnosis of myxedema was made

Thyroid extract was started This produced marked improvement and raised her metabolism to standard normal by September, 1921 On two subsequent occasions, one in June, 1922, and one in August, 1922, when she omitted thyroid for 3 weeks, her rate fell to minus 23 per cent each time, and she became tired and slowed up Her skin became dry and her face expressionless again She resumed thyroid and felt perfectly well On November 9, 1926, at which time her metabolism was minus 11 per cent, thyroid was omitted Her metabolic rate gradually fell, until by March, 1927, it was minus 23 per cent Until June, 1928, a period of 1½ years from the time thyroid was omitted, it ranged from minus 8 to minus 22 per cent, with one observation of zero There was no return of symptoms of myxedema Her hair and skin did not become drier There was no evidence of edema and no decrease in strength and energy She was not slowed up, never felt like sleeping in the daytime, and could do all her own housework without fatigue, rising at 6 a m and retiring at 9 to 10 p m She looked well and insisted that she felt just as well, if not better, than when taking thyroid extract

Case 12 (fig 7) Lab No 2940[10] Mrs E B C Age 48 This patient had a subtotal thyroidectomy for exophthalmic goiter on December 10, 1924 Up to March, 1925, her basal metabolism ranged from minus 10 to minus 16 per cent and she was exceptionally well By May, 1925, her metabolic rate was minus 25 per cent Her memory was failing and she was becoming weak and lethargic Her

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hair was falling out and her voice was becoming husky A diagnosis of myxedema was made Thyroid extract (Burroughs Wellcome), 1½ grains daily, was started and gradually increased to 4 grains daily While on this medication, her metabolism did not rise above minus 7 per cent, and usually ranged in the vicinity of minus 15 per cent She felt well and had no symptoms of myxedema In January, 1927, nearly 2 years after starting it, thyroid was omitted From then until May, 1927, her metabolism ranged from minus 17 to minus 28 per cent, and she felt as well as ever, except for some fatigue attributed to unusually heavy work that she

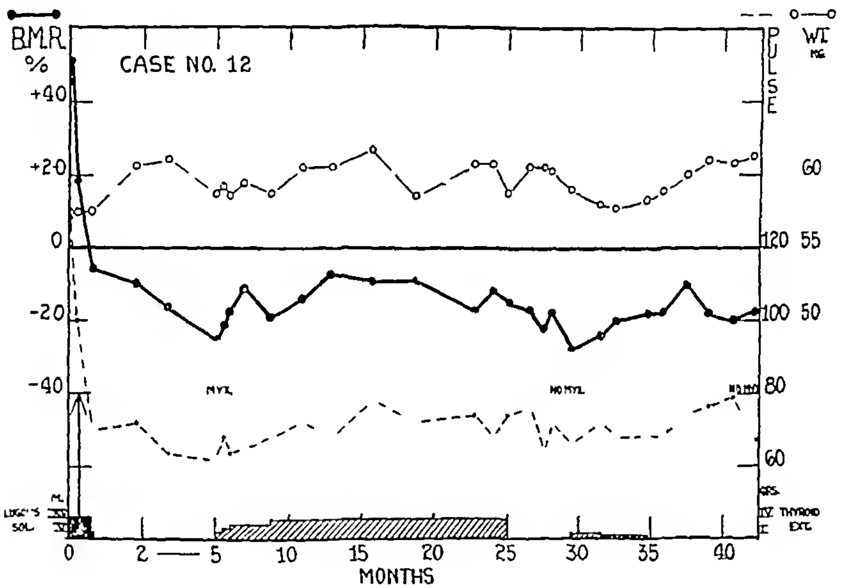

Fig 7 Lab No 2940 Mrs E B C Age 47 Onset of Temporary Myxedema 4 to 5 Months after Subtotal Thyroidectomy (arrow) for Exophthalmic Goiter

For 4 months after first omission, and 7½ months after last omission of thyroid extract, the patient has remained healthy Her basal metabolic rate is low, but apparently this is normal for her

had undertaken at the time of omission of thyroid Thyroid in small doses was given again, without any clinical or metabolic effect In October, 1927, it was omitted for a second time Up to June, 1928, her metabolic rate was still low (minus 18 per cent) and she had experienced no clinical change She had plenty of drive and energy, and was bright and alert She was able to take full care of an 8-room house, run a chicken farm, and do a great deal of church and club work, including lecture tours, without undue fatigue in fact, she could outdo her friends There was no evidence of myxedema

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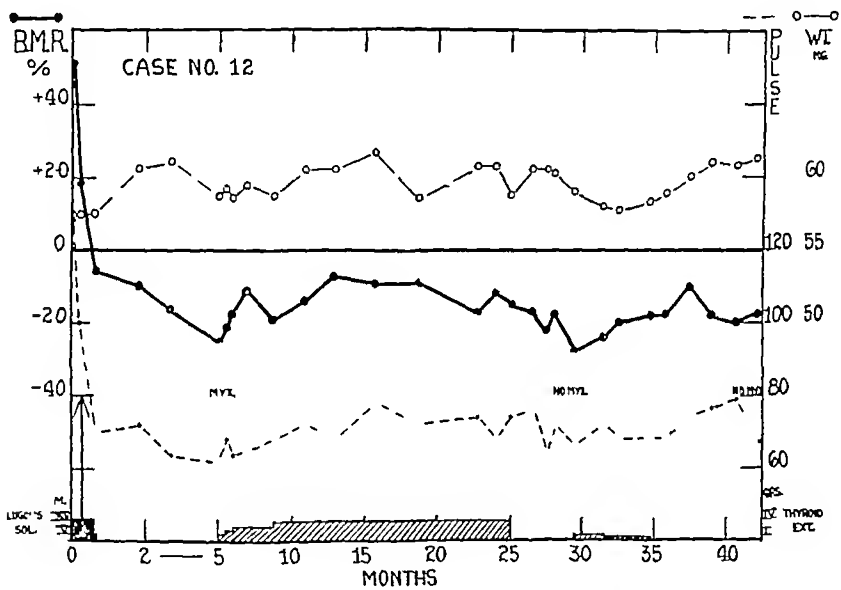

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that of myxedema following subtotal thyroidectomy, i e , about 1 per cent whereas, after x-ray, the incidence was about 4 per cent This suggests that x-ray had a definite influence in causing the myxedema in our series The number of cases on which these figures are based however, is necessarily so small that one cannot place much reliance upon such apparent differences in incidence In any event, the incidence of myxedema following x-ray therapy of the thyroid is not great enough to constitute a contraindication to this form of treatment

If the myxedema be an x-ray effect, it is similar in its late onset to such other x-ray effects as skin atrophy and telangiectasis, and is probably due to a very slow fibrosis of the thyroid gland tissue Skin and gland changes do not go hand in hand however In only one case of this series was there any evidence of skin changes Case 4, treated in the year 1916 before the technique was perfected, shows a small amount of telangiectasis Thus, if the myxedema be due to x-ray therapy, sufficient dosage to destroy thyroid tissue in 5 cases, affected the skin over the gland in only one case On the other hand, we have a patient first treated in the year 1915 who now shows considerable telangiectasis, but who still has thyrotoxicosis If the change produced in the gland is in the nature of a gradual fibrosis, it evidently does not preclude a restoration of gland function at a later date, as shown by case 11 (fig 6), where myxedema occurred over a year after x-ray treatment and persisted for at least 1 year, but did not recur up to $1\frac{1}{2}$ years after omission of thyroid extract Another x-ray effect which might be considered comparable to this is that of restoration of function of the ovaries after it has been suspended by x-ray treatment Here, however, the onset of the ovarian deficiency is immediate, and not delayed, as may be the onset of thyroid deficiency

The fact that the myxedema may be temporary has an important bearing upon thyroid therapy It shows the desirability of periodic omissions of this medication in order to prevent unnecessary administration, in a certain number of cases

SUMMARY AND CONCLUSIONS

1 Myxedema following treatment for thyrotoxicosis may be either temporary or permanent

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often seen After about 20 hours, or sometimes earlier if a meal of meat is eaten, the dogs become definitely ill, refuse to move about unless urged, and usually have fibrillary tremors which can be felt in most of the skeletal muscles Visible twitching of the paws and lips soon follows and becomes more marked during the next 12 hours Violent general convulsions are sometimes seen, especially when aroused by some outside stimulus such as handling At this stage a foul bloody diarrhea is frequently seen with vomiting of black material containing changed or even fresh blood The dogs then grow gradually weaker and the convulsive twitching becomes more feeble or disappears There may be coma, but more often there is a profound weakness with consciousness retained Death most often occurs between 48 and 60 hours after the dose and is usually from weakness or exhaustion but occasionally comes suddenly in the midst of a convulsive seizure Convulsive symptoms are occasionally entirely absent and death follows a period of depression and coma

As has been previously noted by Lamson (1), Meyer and Pessoa (3), and Davis (4), the most obvious damage done by carbon tetrachloride is to the liver At autopsy this organ appears yellowish and the lobules are definitely outlined with red central areas surrounded by yellow tissue On section this same appearance is seen throughout the tissue The liver feels very greasy and is so soft and friable that it can be readily mashed in the fingers Sometimes the lobes contain cracks from which loss of blood into the peritoneal cavity may have reached the proportion of severe hemorrhage This finding is most common in the type of death mentioned above which ensues rapidly in the midst of a convulsive seizure In such cases as much as a liter of blood may be found in the abdominal cavity and this hemorrhage is apparently the immediate cause of death More commonly, however, the liver though congested and friable is not ruptured The gastro-intestinal tract usually contains old blood and sometimes fresh blood is seen oozing from numerous hemorrhagic areas in the pyloric end of the stomach and upper third of the small intestine Congestion in these portions of the tract is very marked and is not due to the local irritation of carbon tetrachloride since the same doses of the drug cause no such condition in adequately protected animals The kidneys show no very striking abnormality though some congestion is often noted

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by the early administration of calcium the majority of dogs can be cured by persistent medication during the 3 or 4 days of severe intoxication

Typical protocols of 2 of about 25 dogs cured by calcium therapy serve to illustrate the usual course of treatment The first dog reported required medication somewhat longer than is usually necessary after receiving 4 cc of carbon tetrachloride per kilogram The case is otherwise perfectly typical and is chosen for presentation here because it illustrates the use of several forms of calcium therapy The second dog required less persistent treatment but in other respects is very similar to the first one Later work has shown the inadvisability of allowing poisoned or convalescent dogs to eat meat but this point was not appreciated at the time of these particular experiments

Protocol, Case T D 11 Brindle and white male, weight 7 9 kgm On low calcium meat diet 2 to 3 weeks before experiment

January 22, 1927

3 00 p m Received 4 cc CCl_4 per kilogram by stomach tube—total dose 31 6 cc

January 23, 1927

9 00 a m Has slight twitching of paws and lips

10 00 a.m Given 100 cc of 5 per cent calcium lactate by stomach tube

2 00 p m Appears very sick, breathing irregularly due to spasmodic contractions of the diaphragm

6 00 p m Has violent tetanic convulsions Given 500 mgm of $CaCl_2$ intravenously as 5 per cent solution

6 30 p m Seems much better—convulsions have ceased entirely

8 00 p m Dog is perfectly quiet, conscious but weak

9 00 p.m Slight muscular twitching reappears Given 350 mgm of $CaCl_2$ intravenously as 1 per cent solution Dog vomited undigested meat eaten two days before

10 00 p.m Seems much better, walks around the room, has no tremor

January 24, 1927

10 00 a.m Seems rather weak but has no convulsive symptoms Given 100 cc of milk and 100 cc 5 per cent calcium lactate by stomach tube

2 00 p.m Condition unchanged Given 150 cc of milk, 100 cc 5 per cent calcium lactate by stomach tube

8 00 p.m Condition unchanged Given 150 cc of milk, 100 cc 5 per cent calcium lactate by stomach tube

January 25, 1927

9 00 a m Has fine tremor in paws Given 100 cc of milk, 50 cc 5 per cent calcium lactate and 1 egg by stomach tube

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Protocol, Case T D 32 Weight 7 8 kgm On low calcium meat diet for 3 weeks before experiment

February 28, 1927
- 3 00 p m Given 4 cc CCl_4 per kilogram by stomach tube—total dose 31 2 cc
- 8 00 p.m Resting quietly

March 1, 1927
- 9 00 a m Good condition
- 10 00 a m Given 50 cc molar NH_4Cl by stomach tube
- 2 00 p m Given 50 cc molar NH_4Cl by stomach tube
- 3 30 p.m Given 100 cc 5 per cent calcium lactate, 100 cc of milk and 1 egg by stomach tube
- 9 00 p m Good condition Given 100 cc 5 per cent calcium lactate by stomach tube

March 2, 1927
- 9 00 a.m Fair condition Given 30 cc molar NH_4Cl, 175 cc of milk and 1 egg by tube—vomited
- 12 15 p m Dog lying on side with violent muscle twitching—is only semi-conscious Given 450 mgm $CaCl_2$ intravenously as 5 per cent solution The twitching stops within 20 minutes and the dog stands up apparently normal
- 8 00 p m Still in good condition Given 50 cc 5 per cent calcium lactate and 100 cc of milk by stomach tube
- 10 00 p m The eight o'clock medication was repeated

March 3, 1927 Dog in good condition Has good appetite and eats a meal of meat, bread, a little milk and 5 grams of a mixture of calcium lactate and carbonate

March 4, 1927 Dog in good condition Eats well, apparently normal

March 5, 1927 Discharged

Of more practical interest than the treatment of poisoned animals is the highly protective action of a preliminary course of a diet high in calcium This is obtained by the daily addition of about 5 grams of a mixture of calcium carbonate and lactate to the meat diet for 1 to 3 weeks before giving carbon tetrachloride From a total of 105 dogs on a low calcium meat diet used for various experiments, 84 died with typical symptoms following 4 cc of carbon tetrachloride per kilogram Of the 21 surviving, 6 were desperately ill for several days, 6 refused to eat meat after the administration of carbon tetrachloride, and 9 showed no serious symptoms In contrast to this 75 from a total of 95 on a diet of meat and calcium salts showed no serious symptoms

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TABLE 1

Icteric indices determined before and at intervals after administration of 4 cc of CCl_4 per kilogram to dogs on high and low calcium meat diets*

Number of dog	Indices observed at indicated time intervals					Final outcome
	Before dose	After dose				
		24 hours	48 hours	72 hours	96 hours	
Low calcium—meat diet						
27–10–3	0		16 8			Died 120 hours
27–10–16	0	3 0				Died 36 hours
27–10–18	0	5 0				Died 40 hours
27–11–14	0	9 0				Died 35 hours
27–11–15	0	6 6	10 6			Died 48 hours
27–11–16	0	7 0	9 3			Died 48 hours
27–11–18	0	11 1				Died 25 hours
27–11–27	0	10 4				Died 24 hours
27–11–29	0	3 0	5 8			Died 70 hours
T D 68	0	3 1	2 6	6 6		Died 90 hours
T D 71	0	1 0	3 5			Died 70 hours
T D 74	0	1 5	10 4			Died 60 hours
T D 75	0	2 5	7 6			Died 49 hours
T D 76	0	2 0	8 0			Died 50 hours
T D 46	0	2 5	9 0			Died 49 hours
T D 45	0	2 7	14 0†			Died 33 hours
T D 59	0		14 3	20 8†		Died 60 hours
T D 61	0	2 0	19 3	23 6		Died 80 hours
T D 62	0	8 2	13 7			Died 54 hours
T D 63	0	5 2	7 5			Died 26 hours
L T 22	0	1 0	5 5	7 7	15 0	Died 110 hours
L T 23	0	2 7	7 2			Died 48 hours
L T 26	0	1 0	4 6	26 0	25 0	Died 98 hours
28–6–3	0	6 3	12 1†			Died 36 hours
28–6–4	0	1 0	2 0	Trace		Recovered
27–10–17	0	0	1 0			Recovered
27–9–1	0		7 0	7 0	3 5	Recovered
29–9–2	0		4 0	3 2	0	Recovered
28–6–1	0	2 8	8 2	2 8		Recovered
28–6–2	0	1 5	3 5	2 0		Recovered
27–11–23	0	4 5	14 0			Killed for tissues
27–11–13	0	8 4	12 0			Killed for tissues
27–11–28	0	5 5	7 8			Killed for tissues

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		24 hours	48 hours	72 hours	96 hours	
Low calcium—meat diet						
27–10–3	0		16 8			Died 120 hours
27–10–16	0	3 0				Died 36 hours
27–10–18	0	5 0				Died 40 hours
27–11–14	0	9 0				Died 35 hours
27–11–15	0	6 6	10 6			Died 48 hours
27–11–16	0	7 0	9 3			Died 48 hours
27–11–18	0	11 1				Died 25 hours
27–11–27	0	10 4				Died 24 hours
27–11–29	0	3 0	5 8			Died 70 hours
T D 68	0	3 1	2 6	6 6		Died 90 hours
T D 71	0	1 0	3 5			Died 70 hours
T D 74	0	1 5	10 4			Died 60 hours
T D 75	0	2 5	7 6			Died 49 hours
T D 76	0	2 0	8 0			Died 50 hours
T D 46	0	2 5	9 0			Died 49 hours
T D 45	0	2 7	14 0†			Died 33 hours
T D 59	0		14 3	20 8†		Died 60 hours
T D 61	0	2 0	19 3	23 6		Died 80 hours
T D 62	0	8 2	13 7			Died 54 hours
T D 63	0	5 2	7 5			Died 26 hours
L T 22	0	1 0	5 5	7 7	15 0	Died 110 hours
L T 23	0	2 7	7 2			Died 48 hours
L T 26	0	1 0	4 6	26 0	25 0	Died 98 hours
28–6–3	0	6 3	12 1†			Died 36 hours
28–6–4	0	1 0	2 0	Trace		Recovered
27–10–17	0	0	1 0			Recovered
27–9–1	0		7 0	7 0	3 5	Recovered
29–9–2	0		4 0	3 2	0	Recovered
28–6–1	0	2 8	8 2	2 8		Recovered
28–6–2	0	1 5	3 5	2 0		Recovered
27–11–23	0	4 5	14 0			Killed for tissues
27–11–13	0	8 4	12 0			Killed for tissues
27–11–28	0	5 5	7 8			Killed for tissues

of any clean-cut difference in the degree of derangement of these functions in the two groups Some cases show a retention of phenoltetrachlorphthalein but these are as likely to be found in one group as the other Furthermore, although there is a very definite decreased tolerance for levulose in the majority of cases which have received carbon tetrachloride there is a disappointing lack of parallelism between the severity of symptoms and the degree of hyperglycemia produced by the ingestion of a given amount of levulose

Blood chemistry *a Bilirubinemia* The determination of bilirubin in the blood serum either by van den Bergh's method (7) or more simply by the determination of the icteric index by a modification of Bernheim's technique (8) furnished data more nearly parallel with the severity of symptoms In table 1 are presented icteric indices determined at intervals after carbon tetrachloride administration to dogs in the high and low calcium groups described above In general the bilirubinemia tends to be much more severe in the animals on low calcium diet than in those protected by high calcium Exceptions to this rule are usually seen in the occasional unexplained atypical cases in each group The retention of bile pigments begins to be noticeable 12 to 20 hours after the dose of carbon tetrachloride, and usually as the bilirubinemia becomes severe the more acute symptoms appear The reason for the lower concentration of bilirubin in the blood of animals on high calcium diets is still unexplained An observation which suggests a possible theory is the much greater tendency for the *tissues* of high calcium animals to appear jaundiced It may be possible that tissues well laden with calcium tend to hold bilirubin, perhaps in combination with calcium, preventing its accumulation in the blood stream

b Blood calcium determinations[1] The total blood calcium levels of normal dogs determined by Clark and Collip's modification of Tisdall's method (9) showed no consistent differences in the two groups and ranged between 10 5 and 12 0 mgm per 100 cc of serum During severe intoxication there is no significant change in the total calcium concentration The figures are within normal limits with a tendency in many cases to average slightly higher than the preliminary level before receiving carbon tetrachloride No data have yet been obtained regarding possible changes in the ionized fraction of the total

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Briefly summarized, the intoxication produced by carbon tetrachloride in susceptible animals is characterized by gastro-intestinal irritation, nervous disturbances and convulsions, followed by weakness, depression, and death There is a retention of bile pigments in the blood and a more or less severe hypoglycemia These symptoms are aggravated by eating meat and may be prevented or cured by the administration of calcium salts

Points of similarity between carbon tetrachloride intoxication and experimental guanidine poisoning

The foregoing pathological picture calls to mind similar ones described in the literature as typical of guanidine poisoning As early as 1876 Gergens and Baumann (16) described the effect of intravenous injections of guanidine sulphate in frogs and mammals Dogs and rabbits showed weakness, fibrillary twitching of muscles, convulsions and death following injection Putzeys and Swaen (17), Fuhner (18) (19) Camis (20) and others contributed numerous studies on the action of guanidine compounds on various parts of the nervous system and on the skeletal musculature of frogs—Fuhner bringing out the antagonism which exists between the actions of calcium salts and guanidine on these structures More extensive mammalian experiments were reported by Watanabe (21) (22) (23) (24) (25) in a series of papers in which he again described the nervous symptoms, studied nitrogen metabolism, and reported that a severe hypoglycemia was induced This he ascribed to a condition of acidosis which he believed was indicated by increased ammonia excretion in the urine Gyorgy and Vollmer (26) however discredited the acidosis theory and found rather a condition of alkalosis and reported that the symptoms of guanidine intoxication can be relieved by the administration of hydrochloric acid either intravenously or by mouth Paton and Findlay (27) studied the intoxication produced by guanidine or methyl guanidine and described symptoms very similar to the tetany seen after parathyroidectomy and believed that the two conditions are identical Perhaps the most complete pharmacological and toxicological study of guanidine compounds which we have is a paper

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from normal during intoxication is increased rather than decreased by the correction Since we wished to keep the volume of blood required for each determination as small as possible in order to make repeated studies on the same animal at short intervals—these corrections were not applied except in a few preliminary observations The figures given in table 3 are the uncorrected values obtained We therefore make no claim for their absolute accuracy within 0 2 to 0 3 mgm per 100 cc of blood We know the values are as a rule slightly high We do however make the point that the rise in color producing substances occurs without a corresponding increase in blood constituents other than guanidine known to give color with the reagent used We believe this rise to be due to an accumulation of guanidine compounds in the blood

A description of our exact procedure which is practically that of Major and Weber (35) follows 10 cc of oxalated blood are precipitated in a 100 cc volumetric flask by the Folin-Wu (37) method for protein precipitation with the single difference that 2/3 N hydrochloric acid is used in place of 2/3 N sulphuric acid Fifty cubic centimeters of the protein free filtrate are evaporated slowly to dryness on a hot plate or steam bath The dry residue is then extracted repeatedly with small amounts of hot absolute alcohol with careful loosening of the residue with a rubber policeman to insure complete extraction of guanidine The successive alcoholic extracts are filtered through a small filter and the total of 30 to 40 cc of filtrate collected in a small beaker and evaporated just to dryness on a hot plate Care should be exercised not to char the residue The residue in the beaker is then dissolved in 5 cc of distilled water and to this solution 1 cc of the freshly prepared guanidine reagent described above is added If the resulting colored solution is not perfectly clear it is shaken with a little powdered barium carbonate and filtered through a small high grade filter paper The clear filtrate is allowed to stand 15 minutes and compared in a colorimeter with an appropriate standard solution of guanidine hydrochloride treated with the same reagent Fifty cubic centimeters of protein free filtrate representing 5 cc of normal blood usually require a standard containing 0 02 mgm of guanidine (calculated as guanidine) in 6 cc Abnormal bloods may require standards as high as 0 2 mgm in the same volume

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The results in table 2 show the accuracy of this procedure in determining guanidine in pure solutions, normal blood, and in blood to which increased amounts of interfering substances have been added

From these figures it appears that only in extreme nitrogen retention could the apparent increase in guanidine be attributed to the interference of the usual blood constituents In repeated tests made by us and in an earlier rather extensive study by Lamson (1) no such retention was found in carbon tetrachloride poisoning

Determination of guanidine and sugar levels in blood of dogs during carbon tetrachloride and chloroform poisoning and after guanidine administration

The method just described was applied to the study of blood samples taken before and at intervals after the administration of carbon tetrachloride to dogs under various conditions which are known to affect the toxicity of the drug These figures, together with blood sugar and icteric index determinations on the same samples, are arranged in groups in table 3 and are discussed separately under appropriate headings

Carbon tetrachloride poisoning with high and low calcium meat diets

There is a tendency for the guanidine content of the blood to increase slightly several hours after the dose of carbon tetrachloride This tendency is much exaggerated if meat is eaten Because of the importance of meat in this respect animals even when on a low calcium diet sometimes escape serious symptoms if they persistently refuse to eat after receiving carbon tetrachloride From the table it is seen that a rise in guanidine is followed within a few hours by a fall in blood sugar The difference in the high and low calcium groups on meat diet (A and B) seems to lie in the severity of the subsequent

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TABLE 3—*Continued*

Dog number	Hours after dose	Guanidine	Blood sugar	Icteric index	Remarks
Group B—Dogs on meat—High calcium diet—4 cc CCl_4 per kilogram					
		mgm	*mgm*		
28-6-7	Preliminary	0 48	100	0	
Weight 7 1 kgm	21 hours	0 48	93		Ate meat + calcium 22 hours after dose
	27 hours	0 51	80	1 0	Good condition
	45 hours	0 45	92	1 0	Ate meat + Ca salts 46 hours after dose
	51 hours	1 33	83		Good condition
	72 hours	0 49	95		Good condition—recovered
28-6-8	Preliminary	0 37	88	0	
Weight 8 4 kgm.	21 hours	0 44	88		Very quiet—refused to eat
	27 hours	0 66	87	9 8	
	45 hours	0 55	78	10 0	Refused to eat
	72 hours	0 89	84	8 6	Ate a little meat + calcium
	96 hours	0 40	90	2 0	Recovered
28-6-9	Preliminary	0 40	95	0	
Weight 8 1 kgm	21 hours	0 40	80		
	27 hours	0 96	95	3 1	Ate meat + calcium at 22 hours
	45 hours	0 50	87	2 5	Ate meat + calcium at 46 hours
	51 hours	0 88	78		
	72 hours	0 46	84	Trace	Well—discharged
28-6-10	Preliminary	0 34	93	0	
Weight 7 0 kgm.	21 hours	0 44	78		Ate meat at 22 hours
	27 hours	0 96	64	3 5	
	45 hours	1 63	69	2 5	Refused to eat
	72 hours	1 71	66	10 8	Very sick
	96 hours	0 80	70	5 0	Much better
	120 hours	0 40	80	2 0	Recovered
28-2-3	Preliminary	0 47	75		
Weight 9 9 kgm.	6 hours	0 50	100		Refused to eat
	24 hours	0 66	43		Very quiet and sick
	48 hours	0 61	42	10 0	Ate meat + calcium salts—very quiet
	72 hours	0 61	68	12 5	
	102 hours	0 30	56		Did not eat
	132 hours	0 33	83		Recovered

TABLE 3—*Continued*

Dog number	Hours after dose	Guanidine	Blood sugar	Icteric index	Remarks
Group B—Dogs on meat—High calcium diet—4 cc CCl_4 per kilogram					
		mgm	*mgm*		
28–6–7	Preliminary	0 48	100	0	
Weight 7 1 kgm	21 hours	0 48	93		Ate meat + calcium 22 hours after dose
	27 hours	0 51	80	1 0	Good condition
	45 hours	0 45	92	1 0	Ate meat + Ca salts 46 hours after dose
	51 hours	1 33	83		Good condition
	72 hours	0 49	95		Good condition—recovered
28–6–8	Preliminary	0 37	88	0	
Weight 8 4 kgm.	21 hours	0 44	88		Very quiet—refused to eat
	27 hours	0 66	87	9 8	
	45 hours	0 55	78	10 0	Refused to eat
	72 hours	0 89	84	8 6	Ate a little meat + calcium
	96 hours	0 40	90	2 0	Recovered
28–6–9	Preliminary	0 40	95	0	
Weight 8 1 kgm	21 hours	0 40	80		
	27 hours	0 96	95	3 1	Ate meat + calcium at 22 hours
	45 hours	0 50	87	2 5	Ate meat + calcium at 46 hours
	51 hours	0 88	78		
	72 hours	0 46	84	Trace	Well—discharged
28–6–10	Preliminary	0 34	93	0	
Weight 7 0 kgm.	21 hours	0 44	78		Ate meat at 22 hours
	27 hours	0 96	64	3 5	
	45 hours	1 63	69	2 5	Refused to eat
	72 hours	1 71	66	10 8	Very sick
	96 hours	0 80	70	5 0	Much better
	120 hours	0 40	80	2 0	Recovered
28–2–3	Preliminary	0 47	75		
Weight 9 9 kgm.	6 hours	0 50	100		Refused to eat
	24 hours	0 66	43		Very quiet and sick
	48 hours	0 61	42	10 0	Ate meat + calcium salts—very quiet
	72 hours	0 61	68	12 5	
	102 hours	0 30	56		Did not eat
	132 hours	0 33	83		Recovered

TABLE 3—*Continued*

Dog number	Hours after dose	Guanidine	Blood sugar	Icteric index	Remarks
Group D—Dogs receiving 4 cc CCl_4 + 4 cc alcohol per kilogram					
		mgm	*mgm*		
28-4-8	Preliminary	0 34*	73	0	
Low calcium meat diet	20 hours	1 06	65	11 7	Ate little meat—vomited it
	25½ hours	0 75	20		Just dead—died quietly
Weight 4 4 kgm					
28-4-9	Preliminary	0 37	78		
Low calcium meat diet	20 hours	0 42	51		Tetanic convulsions
	33 hours	0 66	20		Tetanic convulsions and death
Weight 4 3 kgm					
28-4-11	Preliminary	0 46	78	0	
Low calcium meat diet	20 hours	1 23	78		Ate meat at 21 hours Tremors noted
Weight 5 6 kgm.	43 hours	1 61	50	15 9	In coma—died few minutes later
28-4-12	Preliminary	0 48†	71	0	
Low calcium meat diet	20 hours	0 80	62	4 9	Ate meat at 21 hours
	26 hours	1 60	54		Quite sick—quiet
Weight 4 8 kgm	34 hours	0 83	48		Very sick—barely conscious—died 2-3 hours—later
28-2-20	Preliminary	0 48	86	0	
Mixed diet High calcium	4 hours	0 46	79		Ate meat at 5 hours
	7 hours	0 76	68		
Weight 10 9 kgm	11 hours	1 20	43		Muscle twitching
	24 hours	1 26	25		Very sick—lying on side—muscle twitching
	30 hours	0 87	23	9 3	Violent tetanic convulsions—died shortly after last sample

* The corresponding creatine concentrations for this and the following blood samples of this animal are 3 11, 2 39, and 2 43 mgm per 100 cc of blood respectively

† The corresponding creatine concentrations for this and the following blood samples of this animal are 3 00, 1 25, 1 20 and 1 00 mgm per 100 cc. of blood respectively

TABLE 3—*Continued*

Dog number	Hours after dose	Guanidine	Blood sugar	Icteric index	Remarks
Group D—Dogs receiving 4 cc CCl_4 + 4 cc alcohol per kilogram					
		mgm	*mgm*		
28–4–8	Preliminary	0 34*	73	0	
Low calcium meat diet	20 hours	1 06	65	11 7	Ate little meat—vomited it
	25½ hours	0 75	20		Just dead—died quietly
Weight 4 4 kgm					
28–4–9	Preliminary	0 37	78		
Low calcium meat diet	20 hours	0 42	51		Tetanic convulsions
	33 hours	0 66	20		Tetanic convulsions and death
Weight 4 3 kgm					
28–4–11	Preliminary	0 46	78	0	
Low calcium meat diet	20 hours	1 23	78		Ate meat at 21 hours Tremors noted
Weight 5 6 kgm.	43 hours	1 61	50	15 9	In coma—died few minutes later
28–4–12	Preliminary	0 48†	71	0	
Low calcium meat diet	20 hours	0 80	62	4 9	Ate meat at 21 hours
	26 hours	1 60	54		Quite sick—quiet
Weight 4 8 kgm	34 hours	0 83	48		Very sick—barely conscious—died 2–3 hours—later
28–2–20	Preliminary	0 48	86	0	
Mixed diet High calcium	4 hours	0 46	79		Ate meat at 5 hours
	7 hours	0 76	68		
Weight 10 9 kgm	11 hours	1 20	43		Muscle twitching
	24 hours	1 26	25		Very sick—lying on side—muscle twitching
	30 hours	0 87	23	9 3	Violent tetanic convulsions—died shortly after last sample

* The corresponding creatine concentrations for this and the following blood samples of this animal are 3 11, 2 39, and 2 43 mgm per 100 cc of blood respectively

† The corresponding creatine concentrations for this and the following blood samples of this animal are 3 00, 1 25, 1 20 and 1 00 mgm per 100 cc. of blood respectively

TABLE 3—*Continued*

Dog number	Hours after dose	Guanidine	Blood sugar	Icteric index	Remarks
Group F—Experimental guanidine poisoning—Continued					
		mgm	*mgm*		
28-7-10	Preliminary	0 40	80	0	
Low calcium meat diet	4 hours	3 84	62		Restless, nausea, fibrillary twitching of muscles
Weight 8 1 kgm	6 hours	3 68	51		Extensor spasms when handled
200 mgm guanidine hydrochloride per kgm subcutaneously	8 hours	2 22	42		Quiet unless handled, then convulsions
	11 hours	1 50	37	0	Bloody diarrhea—quiet—unconscious Died few minutes later

hypoglycemia rather than in the concentrations of guanidine reached Further evidence that calcium is responsible for the avoidance of dangerously low blood sugar levels in the animals in Group B is furnished by later experiments (see chart A) in which rapidly falling blood sugar concentrations are maintained above the danger level by the administration of calcium salts One of the few exceptions to the usual rule of low resistance to intoxication in low calcium animals is represented in the second member of Group A In spite of low calcium intake and the production of a high guanidine concentration in the blood a safe blood sugar level is maintained The low icteric index too is like those seen in animals on high calcium diet In the other direction an occasional animal on high calcium diet will succumb with the same symptoms and blood changes shown by animals on deficient calcium diet We have been unable to avoid a few such discrepancies in each group However, when a condition is being studied in which nitrogen, sugar, and calcium metabolisms seem all to be involved this is perhaps not to be wondered at Feeding calcium cannot guarantee its absorption and utilization, nor can dogs with varying previous life histories all be brought to comparable degrees of calcium lack by 2 or 3 weeks of special diet

Carbon tetrachloride poisoning with bread and milk diet To avoid the rise in guanidine produced by eating meat 10 animals were run on bread and milk diet and all gave consistent results Three typical

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Carbon tetrachloride poisoning with bread and milk diet To avoid the rise in guanidine produced by eating meat 10 animals were run on bread and milk diet and all gave consistent results Three typical

chloride which produce similar symptoms do so by producing comparable concentrations of guanidine in the blood To demonstrate this 12 cases of guanidine poisoning have been studied and the concentrations of guanidine in the blood determined All cases gave similar results and three are included in Table 3 as Group F Our figures are in close agreement with those reported by Major, Orr and Weber (38) Although the values range somewhat higher than those usually reached in carbon tetrachloride poisoning they are still of the same general order of magnitude It must also be remembered that in carbon tetrachloride and chloroform poisoning the depression of ionized calcium due to the retention of bile pigments would tend to increase the effect of a given concentration of guanidine above that produced in a normal animal

The effect of calcium on the hypoglycemias seen in carbon tetrachloride intoxication and guanidine poisoning

Looking back to the protocols describing the prompt relief following the administration of calcium salts to dogs with severe carbon tetrachloride intoxication, it seems probable that a large factor in the cures must have been a restoration to normal of the very low blood sugar levels Underhill and Blatherwick (39) (40) have shown that the hypoglycemia after parathyroidectomy can be relieved by calcium administration Watanabe (24) was, however, unable to influence the low blood sugar levels produced by guanidine administration by the subcutaneous administration of calcium lactate We believe that this failure was due to inadequate calcium therapy The subcutaneous administration of calcium lactate is a very slow way of furnishing calcium ions to cases of such acute need as is seen in guanidine poisoning We have found that calcium chloride administered intravenously will usually restore the blood sugar to normal in either carbon tetrachloride or guanidine poisoning Even the administration of calcium chloride by mouth often suffices to check a rapidly falling blood sugar in animals in carbon tetrachloride poisoning Such a restoration is not accomplished by reducing the guanidine concentration because a return to normal blood sugar can be brought about during a period when the guanidine concentration in the blood is steadily rising This point as well as the prompt elevation of blood

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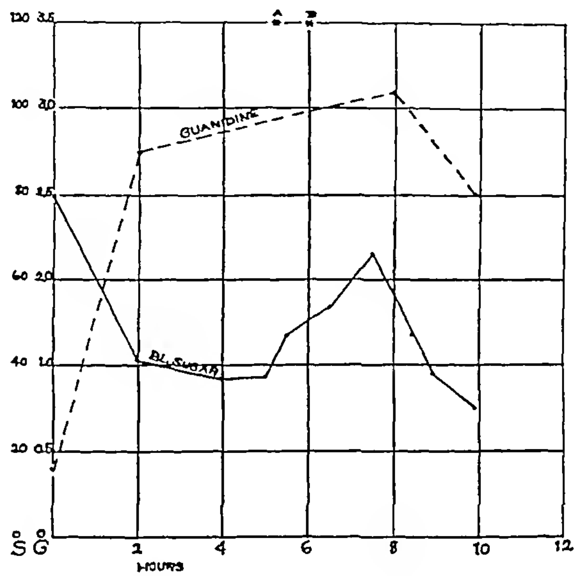

CHART B EFFECT OF CALCIUM ADMINISTRATION ON BLOOD SUGAR CONCENTRATION IN EXPERIMENTAL GUANIDINE POISONING

The figures for blood sugar (*S*) and guanidine (*G*) are in terms of milligrams per 100 cc of blood

Dog no 28–6–19 On low calcium meat diet for 2 to 3 weeks before receiving 200 mgm guanidine hydrochloride per kilogram subcutaneously Typical severe intoxication developed after the administration of the dose

**A*, 500 mgm $CaCl_2$ given intravenously as 10 per cent solution, **B*, 300 mgm $CaCl_2$ given intravenously as 10 per cent solution

The symptoms were much relieved during the time that the blood sugar was elevated After medication was withheld the dog grew rapidly worse, convulsions reappeared, and death occurred 10 hours after the dose with a blood sugar concentration of 30 mgm per 100 cc blood

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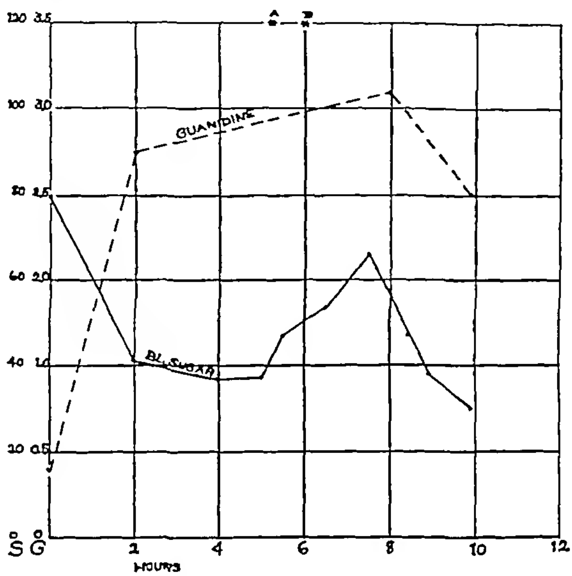

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functional studies already under way will be able to answer the question as to whether these glands have been damaged by the drugs which we know bring about a retention of guanidine Whatever the normal disposal of guanidine is, it seems to be a very effective one because relatively enormous doses of guanidine must be administered to a normal dog to produce a concentration of 2 to 3 mgm of guanidine per 100 cc of blood At present we can only state that both carbon tetrachloride and chloroform cause a serious interference with this mechanism and a retention of guanidine results The toxic symptoms produced by this retained guanidine are very similar to those seen in experimental guanidine poisoning The outstanding features of both intoxications are gastro-intestinal irritation, nervous hyperexcitability followed by depression, extreme hypoglycemia, and death In both conditions calcium has a highly favorable action In carbon tetrachloride poisoning the need for calcium is rendered doubly acute by the increased guanidine and the simultaneous depletion of calcium ions by a retention of bile pigments When this need is met by furnishing calcium most cases of intoxication can be prevented or cured

Practical suggestions regarding the management of a case to be treated with carbon tetrachloride would emphasize first of all the importance of a liberal amount of calcium in the preliminary diet In order to avoid the tendency toward increased guanidine in the blood meat should be avoided and a diet rich in calcium and carbohydrate substituted A bread and milk diet is an easy method of furnishing both calcium and carbohydrate in adequate amounts With these precautions cases of intoxication should be extremely rare If poisoning should occur, a combination of calcium chloride and dextrose therapy seems indicated and in our experience has nearly always proved effective

SUMMARY AND CONCLUSIONS

1 Carbon tetrachloride produces a severe intoxication in dogs on a meat diet which is low in calcium while the addition of calcium salts to the meat diet, or the feeding of a liberal mixed diet without meat causes a high degree of tolerance to the drug Furthermore, cases of poisoning can usually be cured by calcium therapy

2 The outstanding features of the intoxication are gastro-intestinal

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This investigation is one of a series of studies being made under the direction of Dr P D Lamson on the pharmacology and toxicology of carbon tetrachloride The work is being carried on with the support of the International Health Board

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PROCEDURE

In the carrying out of this investigation, two tests for the presence of duodenal contents in the stomach were used, the appearance of bile and the presence of tryptic activity

Twenty-three examinations were made on cases as follows

1–10—total achylia, giving no acid on fractional meals or after injection of histamine (pernicious anemia)
11–14—duodenal ulcer
15—retroperitoneal tumor
16—asthma
17—compression myelitis
18—normal
19–20—simple achylia
21—pyloric obstruction
22—gastroenterostomy

In carrying out the experiments, the contents of the fasting stomach were removed through a Rehfuss tube with the olive located in the lower part of the stomach The stomach was then washed at 3- to 5-minute intervals with small amounts of water or of the regent selected, and samples immediately withdrawn, or the reagent was allowed to remain in the stomach and portions fractioned out at 5- to 10-minute intervals The samples obtained were examined for bile, and tested for the presence of trypsin

Test for trypsin

Principle The samples of gastric content are mixed with purified egg albumin, incubated for 48 hours at 37°, when the digestion mixture is tested quantitatively for free amino groups

Procedure About 15 cc of each sample of gastric content are shaken with permutit to remove ammonia and filtered or centrifuged A few cubic centimeters of the clear liquid obtained should be tested with Nessler's reagent to determine if the ammonia has been completely removed If not, it should be shaken again with permutit and refiltered

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in a graduated test tube in as small an amount as possible of 10 per cent NaOH and water added to make up the desired volume

EXPERIMENTS

The first 10 experiments were on cases of pernicious anemia The first of these is represented in figure 1 The fasting contents were removed and the stomach washed 10 times with 250 cc of water at 37° and completely emptied after each washing Another 250 cc were

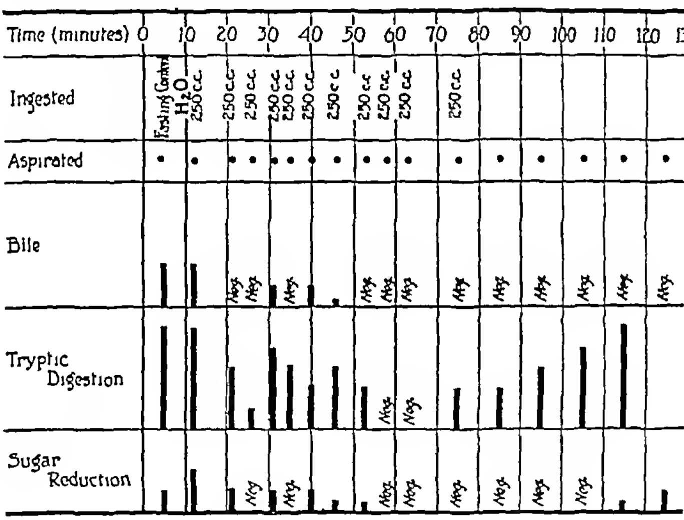

Fig 1 (Experiment 1) Shows the Presence in the Stomach of Trypsin During Repeated Washings with Water, even in the Absence of Bile

Note the increase in trypsin as the stomach empties
Subject Wm F Diagnosis Pernicious anemia Date January 22, 1927

then introduced and samples removed at once and after 10 minute intervals for fifty minutes Three tests were employed for duodenal regurgitation,—the presence of bile, tryptic activity, and the inversion of sucrose The last names was tested for by incubating a few cubic centimeters of each sample with a solution of cane sugar and the solution tested, after four hours, with Benedict's reagent for reducing substances

As may be seen from figure 1 all three tests were positive on the

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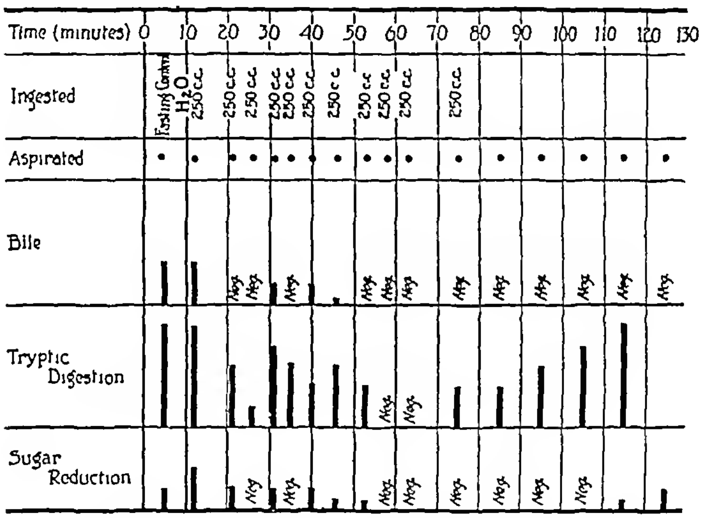

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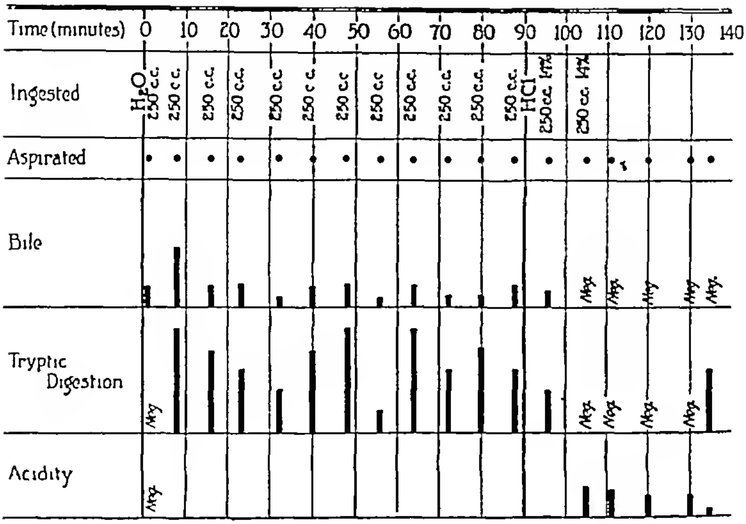


FIG 4 (EXPERIMENT 4) SHOWS THE CONTINUOUS PRESENCE IN THE STOMACH OF BILE AND TRYPSIN DURING WASHINGS WITH WATER, THE ABSENCE OF BOTH WITH DILUTE ACID

Subject Wm F Diagnosis Pernicious anemia Date January 27, 1927

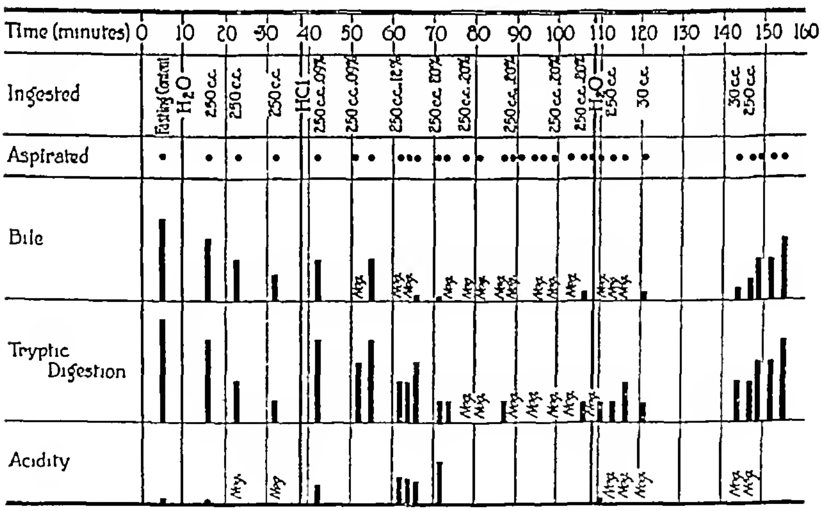
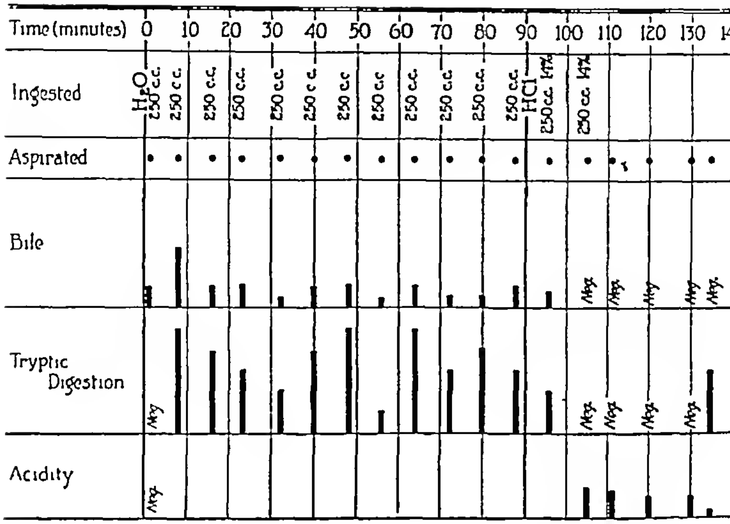


FIG 5 (EXPERIMENT 5) SHOWS THE PRESENCE IN THE STOMACH OF BILE AND TRYPSIN DURING WASHINGS WITH WATER AND DILUTE ACID, THEIR COMPLETE DISAPPEARANCE DURING WASHINGS WITH MORE CONCENTRATED ACID

Subject Wm F Diagnosis Pernicious anemia Date February 5, 1927



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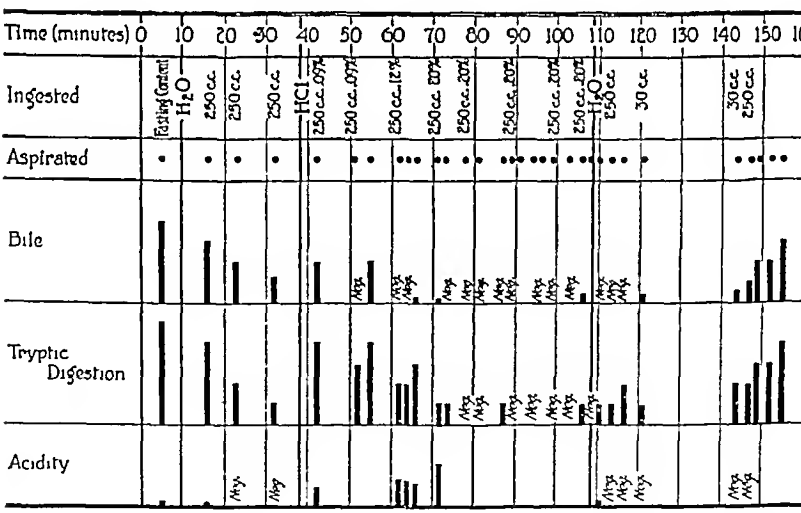

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Subject Wm F Diagnosis Pernicious anemia Date February 5, 1927

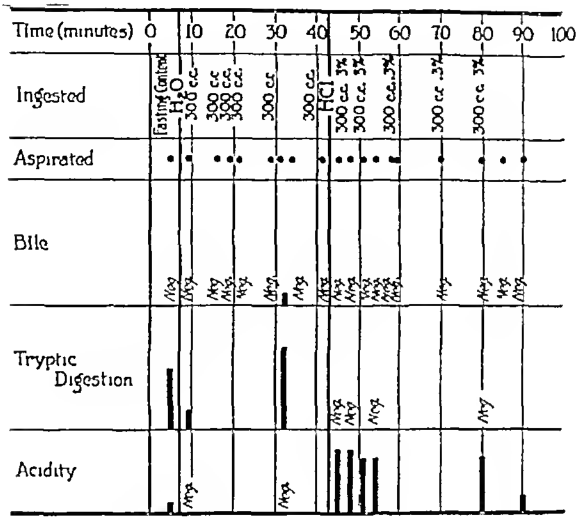


FIG 6 (EXPERIMENT 6) SHOWS THE PRESENCE IN THE STOMACH OF TRYPSIN DURING WASHINGS WITH WATER, ITS DISAPPEARANCE DURING WASHINGS WITH 0 3 PER CENT ACID

Subject Wm W Diagnosis Pernicious anemia Date March 3, 1927

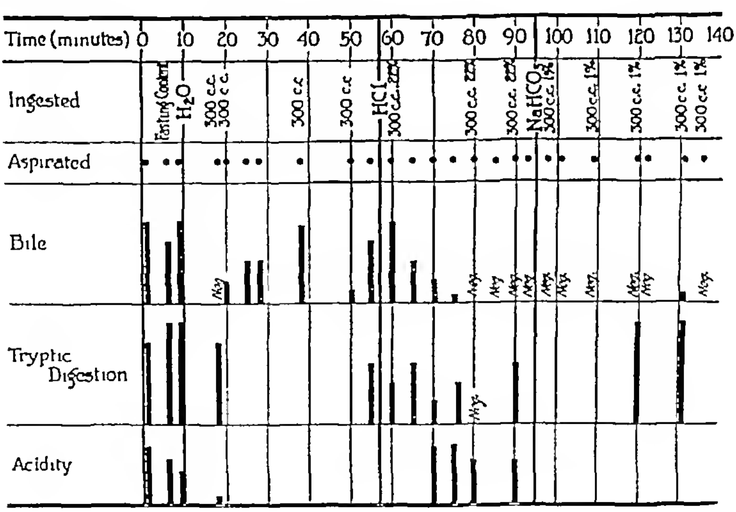
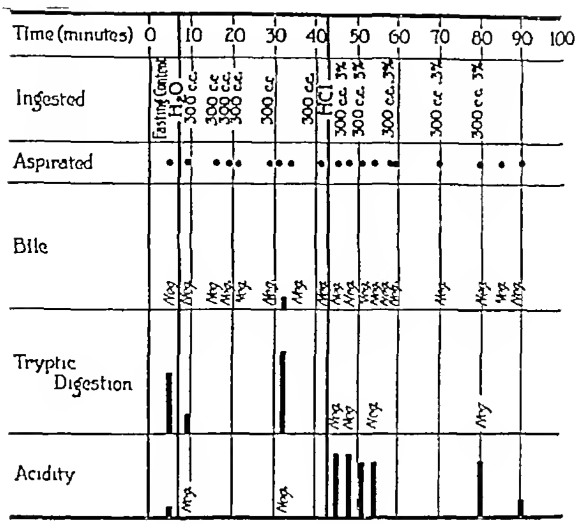


FIG 7 (EXPERIMENT 11) SHOWS THE DECREASE OF BILE IN THE STOMACH DURING WASHINGS WITH ACID, TRYPSIN REMAINING UNCHANGED, RETURN OF BILE AND A MARKED INCREASE OF TRYPSIN ON WASHINGS WITH ALKALI

Subject Axel J Diagnosis Duodenal ulcer Date March 3, 1927



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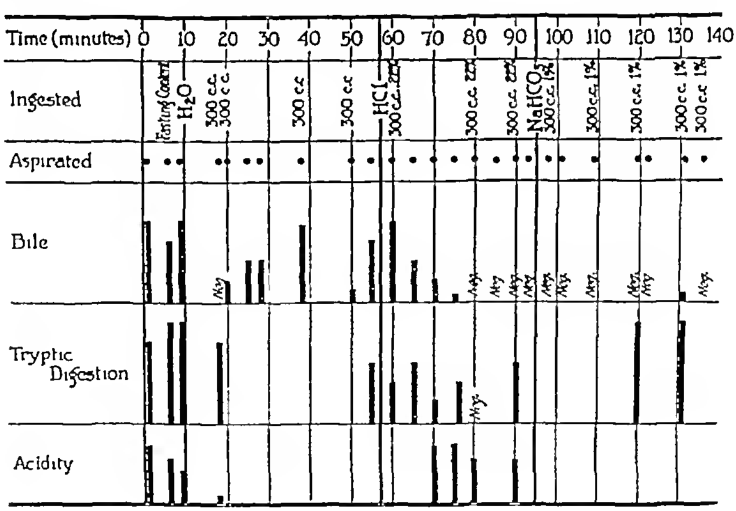
Subject Wm W Diagnosis Pernicious anemia Date March 3, 1927



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(0 3 per cent HCl) and where tryptic activity was lacking entirely during the entire period of acid washing Bile was positive only once, in one of the samples of washing with water

The results of these cases together with four others, nos 7 to 10, are tabulated in table 1 In column 1 are recorded the numbers of the cases In column 2 are shown the appearance or non-appearance of bile and trypsin in the fasting contents, and in the next five columns the numbers of washings with water and with solutions of HCl, together

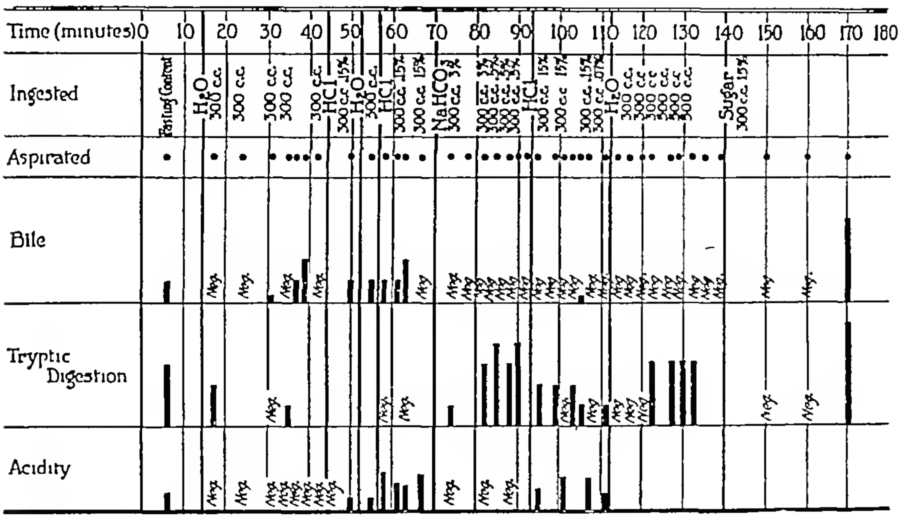

FIG 8 (EXPERIMENT 15) SHOWS THE INDEPENDENT APPEARANCE IN THE STOMACH OF BILE AND TRYPSIN

Subject Wm C Diagnosis Retroperitoneal tumor Date February 17, 1927

with the frequency of the appearance of bile and trypsin in the aspirated samples

Case 11 (fig 7 and table 2) was diagnosed as one of duodenal ulcer Tryptic digestion was present during the entire time except in one acid washing but was somewhat decreased during the entire period of acid ingestion Bile disappeared during the same period and failed to reappear except in traces after 30 minutes of washing with $NaHCO_3$ The other cases (nos 12 to 19), the findings from which are also tabulated in table 2, are of miscellaneous diagnoses other than pernicious anemia

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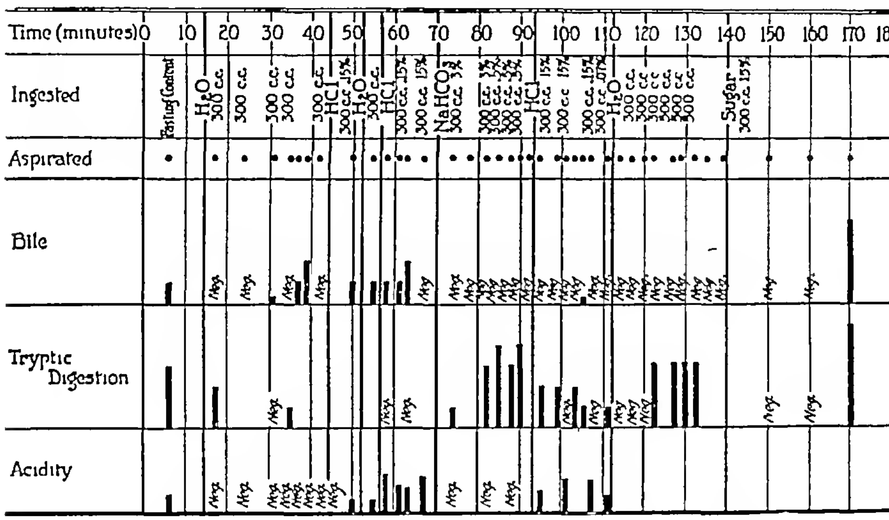

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the gallbladder and the pancreas always flow at the same time, and it seems quite reasonable to assume that one might get gushes of bile containing very little or no pancreatic secretion Further, Baldwin found that an accessory pancreatic duct (fig 10), the duct of Santorini, which opens about three-fourths inch, to one inch, higher up than the common bile duct, was patent to injection in 77 per cent of the cases and patent to dissection in over 85 per cent of the cases that he examined He found also that in some cases this accessory duct was large and apparently performed most of the work, in others it was smaller and sometimes was entirely functionless It seems reasonable to suppose that pancreatic juice might flow to a varying extent through this duct even when the common duct is not functioning and when no bile is getting into the duodenum, and in the cases pictured by Baird, Campbell and Hearn, where a duodenal tube was placed at the level of the ampulla, and the bile removed by continuous aspiration, it may be that bile-free duodenal contents containing pancreatic juice was secreted into the duodenum through the assessory duct and was regurgitated into the stomach

2 Factors affecting the frequency of regurgitation

a Water In tables 3 and 4 are listed the same experiments, together with the number of times regurgitation was observed, as judged by the presence of either bile or trypsin, and the number of times that regurgitation did not occur, as concluded from the fact that both tests were negative

As has been brought out in the preceding paragraphs, regurgitation had occurred in all the fasting contents examined In the washings which followed, regurgitation was found most frequently with the use of water, about the same number of times with sodium bicarbonate, and with decreasing frequency under the influence of acids of increasingly greater concentrations This evidently is not in harmony with Boldyreff

Previous workers have called attention to the frequency of regurgitation when water is used as a test meal Rosemann (1907), for instance, in preparing animals with gastric fistulae for sham feeding, states, "Einmal gewann ich den Eindruck, als ob unter dem Einfluss dieser Spülung (mit distilliertem wasser), besonders leicht ein Zurück-

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solution of HCl introduced into the stomach, lost about 75 per cent of its acidity after an hour, while a 0 3 per cent solution lost 44 per cent and a 0 1 per cent lost about 8 per cent in the same time

On the basis of these and other similar observations Boldyreff (1911) elaborated a definite theory of duodenal regurgitation He states that

TABLE 4

Regurgitation in miscellaneous cases Shows the number of aspirations tested for both bile and trypsin, the number positive for one (indicating regurgitation) and the number negative for both (indicating no regurgitation)

Experiment number	Fasting contents	H_2O			$NaHCO_3$ 1 per cent			HCl, 0 14 per cent			HCl, 0 2 per cent			HCl 0 3 per cent			
		Total number of tests	Number +	Number −	Total number of tests	Number +	Number −	Total number of tests	Number +	Number −	Total number of tests	Number +	Number −	Total number of tests	Number +	Number −	
11	+	2	2	0	2	2	0				6	5	1				Duodenal ulcer
12	+	7	5	2	6	5	1							3	1	2	Duodenal ulcer
13	+	5	5	0	4	4	0							2	0	2	Duodenal ulcer
14	+	2	2	0										6	3	3	Duodenal ulcer
15	+	10	7	3	5	5	0	9	5	4							Retroperitoneal tumor
16	+	6	4	2										2	0	2	Asthma
17	+	2	1	1	3	2	1							5	2	3	Compression myelitis
18	+	3	2	1	5	0	5	2	2	0							Normal
19	+	6	4	2	2	1	1							5	1	4	Simple achylia
Total	9	43	32	11	27	19	8	11	7	4	6	5	1	23	7	16	
Per cent of total	100		74	26		70	30		64	36		83	17		30	70	
23	*	9	9	0	4	4	0							6	6	0	Polya's operation
Per cent of total			100	0		100	0								100	0	

* Not tested

when the gastric content is too acid, or the acid is present in the stomach in too large amounts, the alkaline intestinal juice (especially the pancreatic juice) comes in and neutralizes it The same thing may happen when no acid is introduced, but only gastric juice is present, since the juice as secreted has a much higher acidity (0 5 per cent HCl)

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11	+	2	2	0	2	2	0				6	5	1				Duodenal ulcer
12	+	7	5	2	6	5	1							3	1	2	Duodenal ulcer
13	+	5	5	0	4	4	0							2	0	2	Duodenal ulcer
14	+	2	2	0										6	3	3	Duodenal ulcer
15	+	10	7	3	5	5	0	9	5	4							Retroperitoneal tumor
16	+	6	4	2										2	0	2	Asthma
17	+	2	1	1	3	2	1							5	2	3	Compression myelitis
18	+	3	2	1	5	0	5	2	2	0							Normal
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and doubtful in 4 According to these figures, regurgitation sometimes accompanies high acidity and sometimes is lacking On the other hand, it may be present or absent in cases of achlorhydria

Hicks and Vischer (1915) got regurgitation in 6 out of 30 trials when 150 cc 0 5 per cent HCl was left in a dog's stomach for 15 minutes and in 15 out of 36 trials when left for 30 minutes When 100 cc of acid of lower concentration, i e , 0 4 per cent HCl, was left in the stomach for 20 minutes, no regurgitation occurred in 100 per cent of 10 cases

In our own experiments we did not obtain conclusive results from the use of acid as concentrated as 0 5 per cent HCl, as the patients usually either vomited or felt definite symptoms of gagging, which was invariably accompanied by the passage of bile and pancreatic juice in large amounts through the pylorus We therefore used 0 3 per cent HCl in most of our cases and found that unless large amounts were introduced, gagging seldom occurred In the pernicious anemia cases, the tolerance to acids was especially low, and in one instance even 0 09 per cent HCl could not be used

As stated above, regurgitation occurrred less frequently when acid was introduced, than when water or alkali In the pernicious anemia cases (table 3), regurgitation occurred in 100 per cent of the fasting contents, in 92 per cent of the water washings, 91 per cent of the 0 09 per cent HCl samples, and 62 per cent, 44 per cent and 31 per cent with 0 14 per cent, 0 2 per cent and 0 3 per cent HCl solutions respectively The records for the miscellaneous cases (table 4) are not dissimilar, except that the frequency of regurgitation in the presence of water is somewhat less, (74 per cent), indicating that the atonic sphincter of pernicious anemia reacts to the slight stimulus of water less readily than does the normal

The discrepancy between our results and Morse's may possibly be explained in another way As will be recalled, he found greater regurgitation with higher concentrations of acids Morse examined his aspirated solutions for bile but not for pancreatic juice He judged regurgitation in the absence of bile solely by measuring the relative amounts of gastric content recovered after one-half hour He apparently does not consider the different rates at which water and acids are normally discharged from the stomach It has been shown by Ivy (1918) that water in both man and dogs begins to leave the stom-

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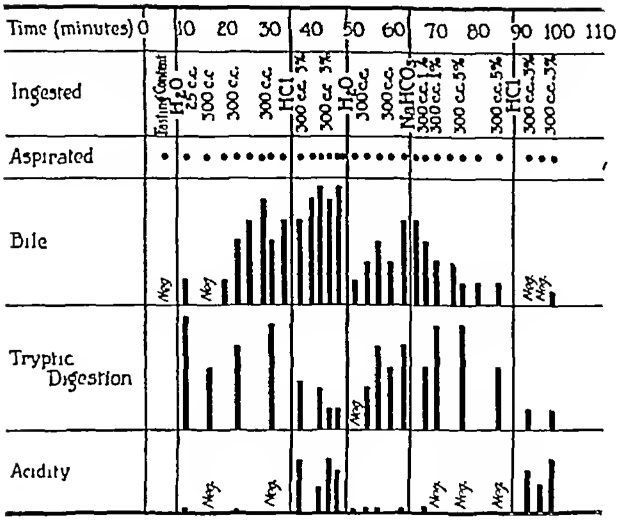


FIG 9 (EXPERIMENT 23) SHOWS THE CONSTANT PRESENCE IN THE STOMACH OF DUODENAL CONTENT AFTER GASTROENTEROSTOMY

Subject Chas C Diagnosis Polya's operation for pyloric carcinoma Date April 16, 1927

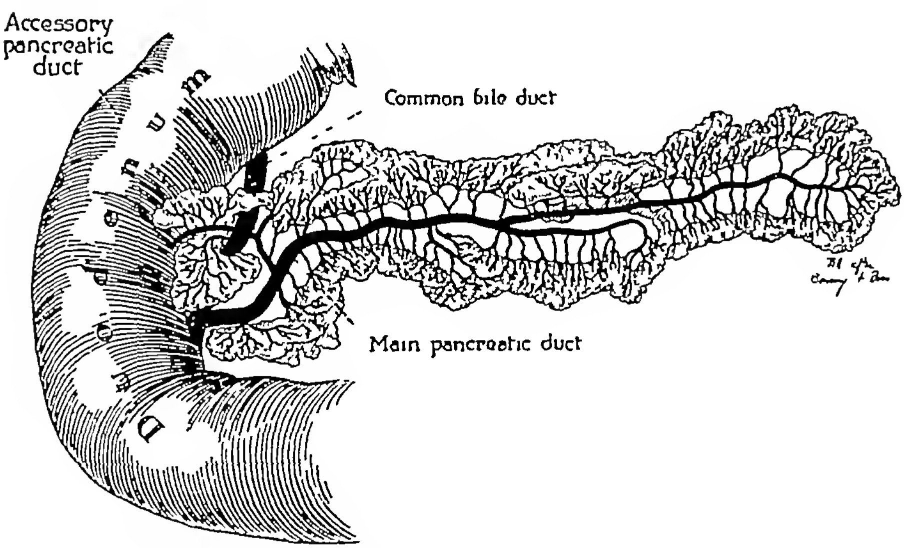
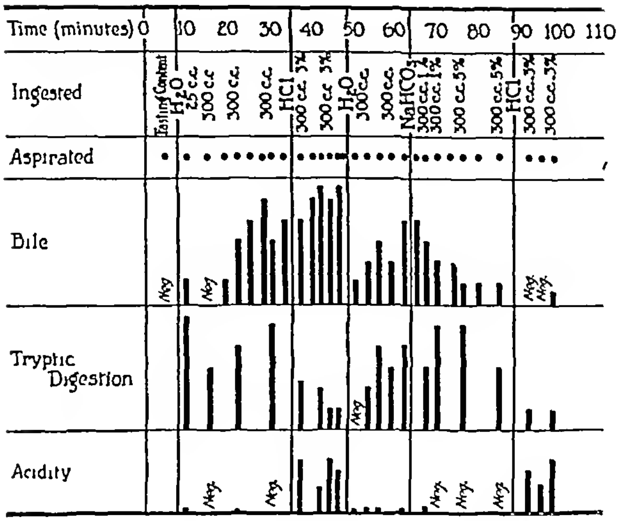


FIG 10 USUAL RELATION OF COMMON BILE DUCT AND PANCREATIC DUCTS



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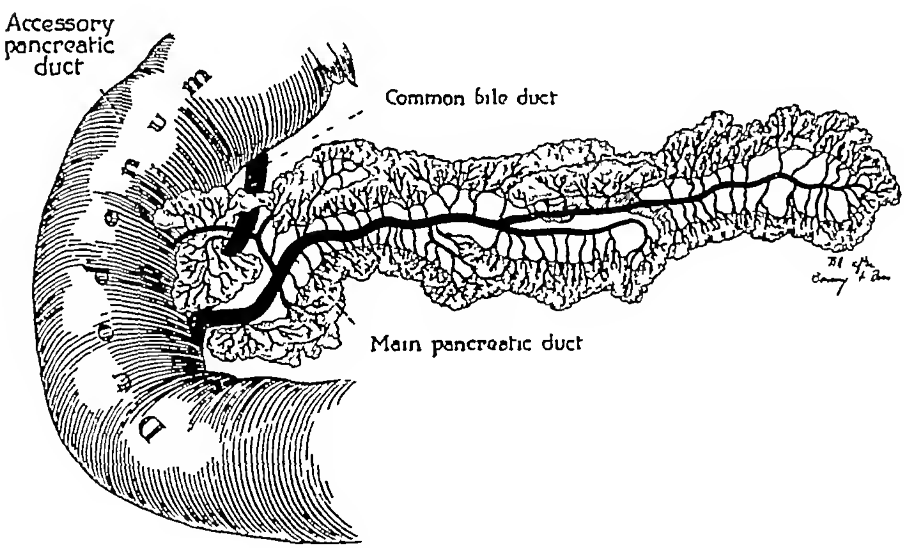

FIG 10 USUAL RELATION OF COMMON BILE DUCT AND PANCREATIC DUCTS

this tonus still more Large amounts (250 to 400 cc) of HCl of higher concentrations, 0 4 to 0 5 per cent, especially in the case of pernicious anemia patients, affects a different mechanism, the vomiting reflex or possibly merely gagging

TABLE 5

Regurgitation with fractional test meals

Experiment number	Diagnosis	Fasting content		H_2O				Fraction						Nature of meal
		Bile	Trypsin	Total number of tests	Number +	Number −		1	2	3	4	5	6	
14	Duodenal ulcer	−	+	7	5	2	Bile	−	+	+	+			Cane sugar
							Trypsin	+	+	+	+			
15	Retroperitoneal tumor	+	+	10	7	3	Bile	−	−	+				Glucose
							Trypsin	−	−	+				
16	Asthma	−	+	6	4	2	Bile	−	−	−	−	−	−	Albumin
							Trypsin	+	+	+	+	+	+	
17	Compression myelitis	−	+	2	1	1	Bile	−	−	−	−	−	−	Glucose
							Trypsin	+	+	+	+	+	+	
18	Normal	−	+	3	2	1	Bile	−	−	−	−	−	+	Glucose
							Trypsin	−	−	−	−	−	−	
19	Simple achylia	+	+	11	9	2	Bile	−	+	+	+	−	−	Glucose
							Trypsin	−	−	−	−	−	+	
20	Simple achylia	+	+	6	4	2	Bile	−	−	−	−	−		Albumin
							Trypsin	+	+	+	+	+		
21	Pyloric obstruction	+	+	2	2	0	Bile	−	−	−				Gruel
							Trypsin	−	+	+				
22	Pernicious anemia	+	+	6	6	0	Bile	−	−	−	−			Gruel
							Trypsin	+	+	+	+			

These views are supported by our findings with fractional test meals In table 5 are recorded the data from 9 such experiments, either with solutions of sugar or albumin or gruel

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Experiment number	Diagnosis	Fasting content: Bile	Fasting content: Trypsin	H_2O: Total number of tests	H_2O: Number +	H_2O: Number −		Fraction: 1	2	3	4	5	6	Nature of meal
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							Trypsin	+	+	+	+			
15	Retroperitoneal tumor	+	+	10	7	3	Bile	−	−	+				Glucose
							Trypsin	−	−	+				
16	Asthma	−	+	6	4	2	Bile	−	−	−	−	−	−	Albumin
							Trypsin	+	+	+	+	+	+	
17	Compression myelitis	−	+	2	1	1	Bile	−	−	−	−	−	−	Glucose
							Trypsin	+	+	+	+	+	+	
18	Normal	−	+	3	2	1	Bile	−	−	−	−	−	+	Glucose
							Trypsin	−	−	−	−	−	−	
19	Simple achylia	+	+	11	9	2	Bile	−	+	+	+	−	−	Glucose
							Trypsin	−	−	−	−	−	+	
20	Simple achylia	+	+	6	4	2	Bile	−	−	−	−	−		Albumin
							Trypsin	+	+	+	+	+		
21	Pyloric obstruction	+	+	2	2	0	Bile	−	−	−				Gruel
							Trypsin	−	+	+				
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							Trypsin	+	+	+	+			

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tion limit, urea excretion proceeds at maximum speed, and the output per minute represents the urea content of a maximum blood volume This blood volume, averaging in normal men about 75 cc per minute, we shall for convenience term the *maximum blood urea clearance, or simply the maximum clearance* It represents the volume of blood which one minute's excretion suffices to clear of urea when the urine volume is large enough to permit a maximum urea output The value of the maximum clearance, C_m, is calculated from the observed urea concentrations of the blood and urine, B and U, and the urine volume, V, in cubic centimeters per minute, by the formula,

$$\textit{Maximum clearance} = C_m = \frac{UV}{B}$$

The concentration ratio, $\frac{U}{B}$, indicates the number of cubic centimeters of blood the urea content of which is represented in 1 cc of urine $\frac{U}{B} \times V$ therefore indicates the number of cubic centimeters of blood represented in the urea content of the V cubic centimeters of urine excreted in 1 minute

Below the augmentation limit the volume of blood, the urea content of which is represented in one minute's excretion, (the blood urea clearance per minute) is not a constant, but varies, on the average, in proportion to the square root of the urine volume In order to compare excretions below the augmentation limit, therefore, they must either be observed with a standard, constant, urine volume output, or, if observed with other urine volumes, the excretion rates must be corrected for the urine volume effect It is practically impossible to fix the urine volume at a definite standard, but, by means of the square root rule of Austin, Stillman, and Van Slyke, the urea excretion that would accompany such a standard urine volume can be calculated from the excretion measured with any other volume below the augmentation limit

The formula for the calculation is developed as follows

If C is the observed blood urea clearance (the cubic centimeters of blood, the urea content of which is excreted in 1 minute) with any

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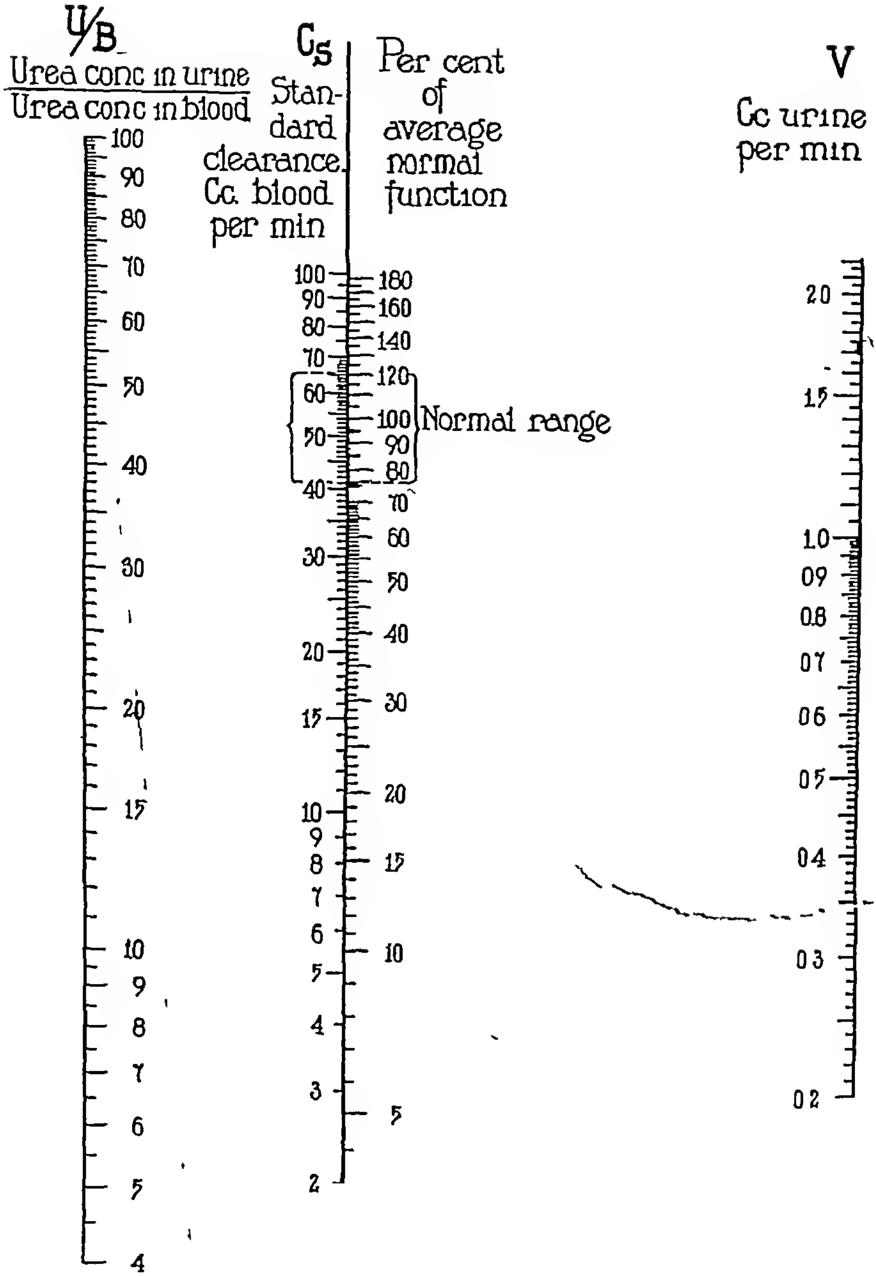
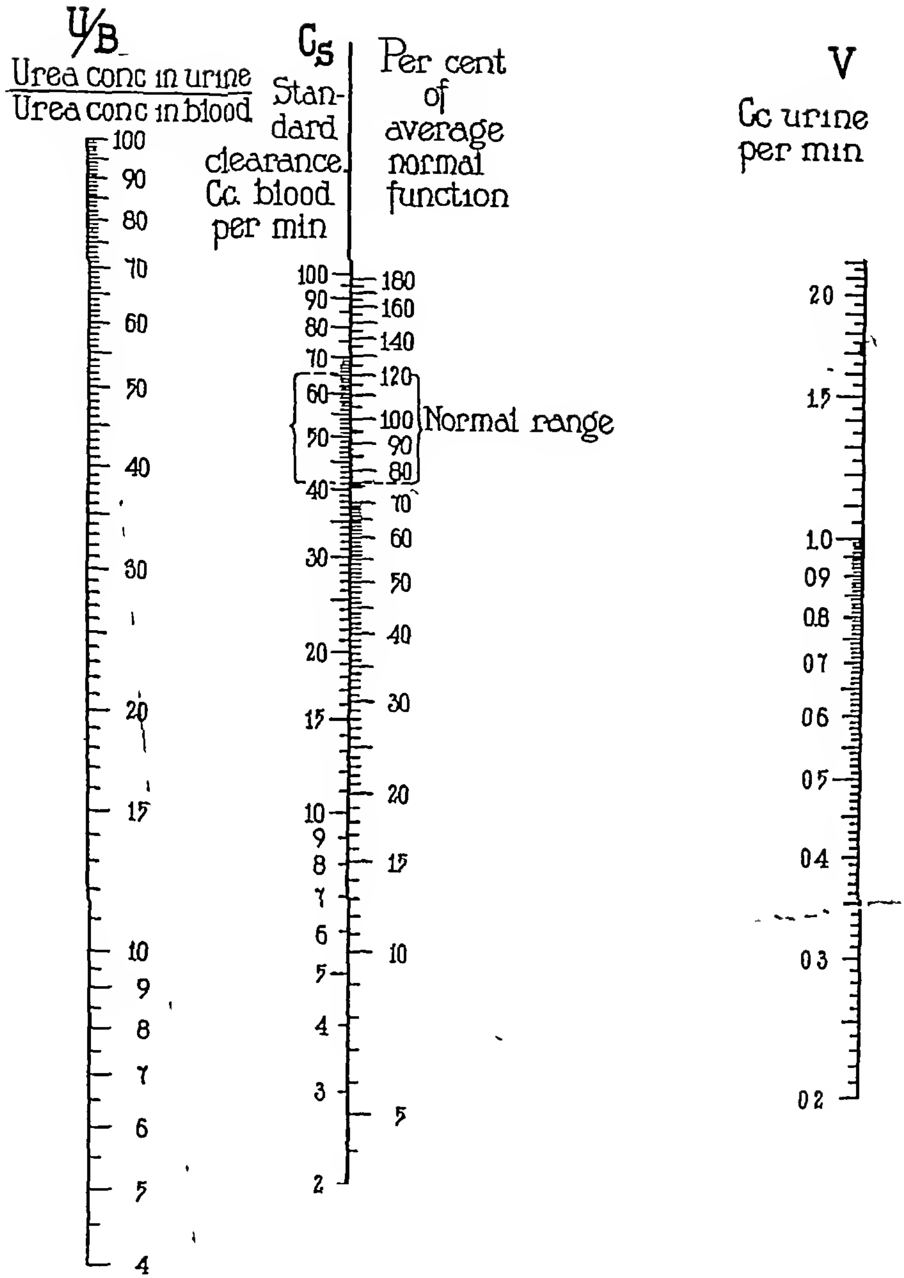


FIG 1 LINE CHART FOR CALCULATING MAXIMUM BLOOD UREA CLEARANCE $C_m = \frac{U V}{B}$, FROM U, B, AND VALUES OF V ABOVE THE AUGMENTATION LIMIT

Connect observed U/B and V values by a straight line Where the line cuts the inner scale read C_m value or per cent of average normal renal function

For subjects differing markedly from usual adult size, a correction is introduced by multiplying the observed V value by the factor $\frac{1\ 73}{\text{sq m surface area}}$ (see next paper), and using the V value thus corrected for the calculation of C_m



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of urea excretion with high urine volumes The maximum clearance is normally about 40 per cent greater than the standard clearance, the mean values being 75 cc of blood per minute for the maximum and 54 cc for the standard Usually, though not always, in pathological conditions both values are affected to approximately the same degree

For use in the above formulae for calculating C_s and C_m, any convenient units of urea or urea N concentration, e g grams per liter, milligram per 100 cc, may be used to express the urea concentrations, U and B so long as the *same* unit is used for both U and B This follows from the fact that in each formula U and B appear only in the ratio $\frac{U}{B}$, so that both U and B may be multiplied by any factor without changing the value of $\frac{U}{B}$ ratio, or of the C_s or C_m calculated therefrom

The unit for expressing values of V, however, can not be changed without changing the numerical values of C_s and C_m

CALCULATION OF CLEARANCE VALUES

If the urine volume exceeds 2 cc per minute, as observed in an adult, or as corrected for body size (see next paper) in a child, the *maximum clearance* is calculated

If the volume thus observed or corrected is less than 2 cc per minute, the *standard clearance* is calculated

It is advantageous as a rule to calculate both clearances in percentages of the mean normal C_s and C_m Urea excretions observed with ordinary urine volumes and calculated in terms of C_s are thus rendered directly comparable with excretions observed with large urine volumes and hence calculated in terms of C_m Furthermore the percentage values thus calculated express directly percentages of average normal renal efficiency

The percentage of average normal C_m is obtained by dividing the absolute C_m value by the mean normal C_m, 75, and multiplying by 100 Similarly the percentage of average normal C_s is obtained by dividing the absolute C_s by 54 and multiplying by 100

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$$C_m = \frac{UV}{B} = \frac{321 \times 3\ 5}{15\ 6} = 72 \text{ cc of blood cleared of urea per minute}$$

Per cent of average normal function = 1 33 × 72 = 96 per cent

Example of calculation of a normal standard clearance

Blood urea N = 14 7 mgm. per 100 cc = B
Urine urea N = 750 mgm. per 100 cc. = U
Urine volume = 50 cc per hour
= 0 83 cc per minute = V

$$C_s = \frac{U\sqrt{V}}{B} = \frac{750 \times 0\ 91}{14\ 7} = 46 \text{ cc of blood cleared of urea per minute}$$

Per cent of average normal function = 1 85 × 46 = 85 per cent

Technique for determining the blood urea clearance as a measure of renal efficiency The necessary data are the concentrations of urea in blood and urine, and the volume of urine excreted in a measured time The manner in which these 3 values are secured may be varied to suit conditions As a routine procedure, however, we have found the following satisfactory

The subject is not subjected to any previous routine, except that vigorous exercise is avoided and the previous meal should be a moderate one, preferably without coffee, which Addis and Drury (1923) have found may increase the blood urea clearance The most desirable time of day, when excretion is least liable to fluctuations, is found according to MacKay (1928) in the hours between breakfast and lunch The patient remains quiet while the urine is collected during two succeeding periods of 1 hour each The chief source of error is probably the possibility of incomplete emptying of the bladder, either at the beginning or end of a period The collection of two urine specimens affords a check on this factor A few minutes before the end of the first hour a blood sample is drawn Its urea content is used for calculation of the clearances during both periods This usage is permissible, because under the conditions of the test the blood urea does not change greatly during an hour

The maximum clearance is calculated if the urine volume observed in an adult, or if the corrected volume $V \times \frac{1\ 73}{\text{Sq m surface area}}$

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very large doses of adrenalin The effect of adrenalin, however, was shown in rabbits by Addis, Barnett, and Shevky (1918) to vary with the dosage, up to a certain maximum it increased urea output, but greater amounts depressed the output Ordinarily Addis (1917) believed that adrenalin and pituitrin act as antagonists in regulating renal activity

Such influences may vary the blood clearence per minute in either of two ways They may vary the renal blood flow without altering the percentage of blood urea removed at each passage through the kidneys Or they may so influence the activity of renal cells that variations do result in the percentage of blood urea removed at each passage The questions, whether and how the percentage of urea removed from the blood in the kidneys can be influenced, awaits experimental proof

It is evident that the urea excretion rate is influenced by other factors in addition to blood urea content and urine volume, and that an erroneous impression would be created by the clearance formulae if they were assumed to express with mathematical exactness the complete effects of all factors influencing urea excretion The width of the range of normal variation indicates the contrary The formulae are only expressions of the effects of two factors, blood urea content and urine volume, which are in continual action and appear to be ordinarily of chief importance in regulating the urea output

To minimize variations due to other factors Addis (1922) in determining the maximum clearance gives water and urea to the fasting subject at the beginning of a 6 hour period, and analyzes specimens of blood and urine collected during the last 3 hours of the period, during which diuresis is maintained by water drinking In determining the standard clearance in this laboratory we have thus far set no conditions, except that the subject should be at rest and should have avoided coffee and other obvious diuretics during the preceding hours of the day The limits of variation in our results, reported below, apply to these conditions It appears possible that by standardizing conditions more completely the range of variation could be narrowed

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output per 24 hours, and noted the rapidity with which the superimposed amount of nitrogen was excreted The procedure was, however, laborious, the results not very consistent The method was abandoned, to be revived occasionally by later authors

Other authors turned their attention to the blood urea, and neglected the excretion The determination of blood urea was introduced into clinical medicine by Strauss (1902) and by Widal and Javal (1904) For diagnostic purposes determination of blood urea concentration has an advantage over determination of urine concentration, in that with ordinary urine volumes the blood figure is less dependent on fluctuations of water output Other factors being constant, however, the blood urea content is proportional to the rate of protein catabolism If a given subject breaks down into urea half as much protein daily his average blood urea will be half as high, given a constant urine volume If the urine volume increases within the ordinary range (below the augmentation limit), the blood urea will be further diminished, increased water output washing out more urea from the blood Both of these factors are likely to be operative in nephritis to prevent a rise in blood urea proportional to renal destruction MacKay and MacKay (1927) in fact report data (which our own confirm) showing that many nephritics do not show blood ureas definitely above the normal maximum until more than 60 per cent of renal function has been lost

The conception of comparing simultaneous urea determinations in blood and urine was introduced by Gréhant (1904) who used the concentration ratio $\frac{U}{B}$ as an expression of renal functional ability However, the immense effects of urine volume changes on the urea concentration, U, in urine were not considered, in consequence of which even approximate constancy can not be obtained with this ratio The use of the $\frac{U}{B}$ ratio was revived by Harrison (1922), who emphasized that the most consistent results were gained when the urine volumes were below 150 to 100 cc per hour This restriction reduces the inconsistencies introduced into the $\frac{U}{B}$ ratio by urine volume changes, but also limits the conditions under which observations can be made

Ambard and Weill (1912) were the first to include both urea output and urine volume in attempting quantitatively to relate urea excretion to blood content They found that urea excretion in normal subjects, and also in nephritics, was governed by two laws, relating output to blood and urine concentrations respectively These laws were combined into the urea excretion formula of Ambard and Weill (1912), which, with numerical constants omitted, is

$$K = \frac{B}{\sqrt{D}\sqrt{U}}$$

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In the present paper we confirm these results on normal subjects, and in an accompanying paper we show that they hold true for nephritics also

H MacLean and de Wesselow (1919, 1920) in the interest of simplicity reverted to a single determination, the urea concentration in the urine, as a test of renal function These authors prescribed certain standard conditions for its determination, designed to make the values more consistent They gave 15 grams of urea with 100 cc of water, and noted whether or not the urine urea concentration in the 2 subsequent hours rose above 2 per cent If it did, they considered the kidneys fairly efficient Gross errors due to dilute urines were excluded by rejecting tests in which the second hour's urine volume exceeded 150 cc Their procedure was admirably adapted to its primary purpose, the rapid examination of large numbers of soldiers In the study of nephritic patients, however, the method invites error by neglect of the blood urea For example, if urinary function is so low that only a tenth the normal blood volume is cleared of urea per hour, the urea output will nevertheless be normal if the blood urea concentration is ten-fold the ordinary Hence the urinary concentration will also be normal, if the volume is not increased For this reason, in the terminal stages of nephritis, with high blood urea content, a urinary urea concentration within ordinary normal ranges may be observed, despite tremendously reduced renal ability[2] The interpretation of figures for urea concentration in urine is therefore uncertain, unless the blood urea content is known, as well as the urine volume

The historical sequence in which the different urea determinations were introduced as indicators of renal function, and the conditions under which they were best applicable, are summarized in table 1

Numerical relation of the present standard clearance to previously used forms of the Austin-Stillman-Van Slyke formula The formula $\frac{U}{B}\sqrt{V}$ expresses the number of cubic centimeters of blood *of which the urea content is concentrated into 1 cc of urine,* when urine excretion is at the average normal rate of 1 cc per minute The mean normal numerical value of 54 indicates that under these conditions the kidneys concentrate the blood urea 54-fold The standard clearance thus may be interpreted as a measure of the concentrating power, as well as the excreting ability, of the kidney For this reason the value now called the standard clearance has, in a number of papers from this laboratory (e g Hiller, McIntosh, and Van Slyke (1927)) been called the "*concentration index*" The term "standard clearance" is at pres-

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In the above papers the formula used in calculating the "index" was $\frac{U}{B}\sqrt{\frac{V}{W}}$ instead of $\frac{U}{B}\sqrt{V}$ However, in the $\frac{V}{W}$ ratio used the volume unit was cubic centimeters per hour per kilogram, which, for a person of 60 kgm weight, is the same as cubic centimeters per minute Hence the values of $\frac{U}{B}\sqrt{\frac{V}{W}}$ in the above papers are approximately interchangeable with those of the present $C_s = \frac{U}{B}\sqrt{V}$ They deviate therefrom in proportion as $\sqrt{W}$ deviates from $\sqrt{60}$, but the fact that unusually low or high body weights influence the value $\frac{U}{B}\sqrt{\frac{V}{W}}$ only in proportion to their square roots, and not their first powers, diminishes the effect on the calculated clearance E g, a person of 50 kgm would weigh 17 per cent less than one of 60, but the effect of this weight difference on the value of the index $\frac{U}{B}\sqrt{\frac{V}{W}}$ is only 9 per cent Our present practice, discussed in the next paper, is to correct for wide divergence from average size by multiplying V by the factor $\frac{1\ 73}{\text{Sq m surface area}}$

The standard clearance $\frac{U}{B}\sqrt{V}$ is, except for omission of the weight correction, identical with the excretion constant $\frac{D}{B\sqrt{VW}}$ of Austin, Stillman and Van Slyke If in $\frac{D}{B\sqrt{VW}}$ the factor D is replaced by its equivalent, UV, the formula changes to $\frac{U}{B}\sqrt{\frac{V}{W}}$ Omission of the weight correction, W, simplifies it to $\frac{U}{B}\sqrt{V}$ The original numerical values of the excretion constant $\frac{D}{B\sqrt{VW}}$, or $\frac{U}{B}\sqrt{\frac{V}{W}}$, of these authors differed from the present clearance, and from the above discussed concentration index, because a different urine volume unit, $\frac{V}{W}$ = liters per 24 hours per kilogram, was used A given excretion rate expressed in cubic centimeters per minute is represented by a figure $\frac{1000\ W}{1440}$, or 0 694 W, times as large as that ex-

ent preferred, partly because when used in conjunction with "maximum clearance" it suggests more clearly the difference in conditions under which the two respective urea excretion rates are determined

In the above papers the formula used in calculating the "index" was $\frac{U}{B}\sqrt{\frac{V}{W}}$ instead of $\frac{U}{B}\sqrt{V}$ However, in the $\frac{V}{W}$ ratio used the volume unit was cubic centimeters per hour per kilogram, which, for a person of 60 kgm weight, is the same as cubic centimeters per minute Hence the values of $\frac{U}{B}\sqrt{\frac{V}{W}}$ in the above papers are approximately interchangeable with those of the present $C_s = \frac{U}{B}\sqrt{V}$ They deviate therefrom in proportion as $\sqrt{W}$ deviates from $\sqrt{60}$, but the fact that unusually low or high body weights influence the value $\frac{U}{B}\sqrt{\frac{V}{W}}$ only in proportion to their square roots, and not their first powers, diminishes the effect on the calculated clearance E g, a person of 50 kgm would weigh 17 per cent less than one of 60, but the effect of this weight difference on the value of the index $\frac{U}{B}\sqrt{\frac{V}{W}}$ is only 9 per cent Our present practice, discussed in the next paper, is to correct for wide divergence from average size by multiplying V by the factor $\frac{1\ 73}{\text{Sq m surface area}}$

The standard clearance $\frac{U}{B}\sqrt{V}$ is, except for omission of the weight correction, identical with the excretion constant $\frac{D}{B\sqrt{VW}}$ of Austin, Stillman and Van Slyke If in $\frac{D}{B\sqrt{VW}}$ the factor D is replaced by its equivalent, UV, the formula changes to $\frac{U}{B}\sqrt{\frac{V}{W}}$ Omission of the weight correction, W, simplifies it to $\frac{U}{B}\sqrt{V}$ The original numerical values of the excretion constant $\frac{D}{B\sqrt{VW}}$, or $\frac{U}{B}\sqrt{\frac{V}{W}}$, of these authors differed from the present clearance, and from the above discussed concentration index, because a different urine volume unit, $\frac{V}{W}$ = liters per 24 hours per kilogram, was used A given excretion rate expressed in cubic centimeters per minute is represented by a figure $\frac{1000\ W}{1440}$, or $0\ 694\ W$, times as large as that ex-

been questioned by Addis and his collaborators Addis and Drury (1923) studied the relationship between V and the excretion ratio (or blood urea clearance) They found that in rabbits changes in volume down to 2 cc per hour had no influence on the observed clearance, $\frac{UV}{B}$ Of the 3 human subjects studied, however, only one was observed with urine volumes below 120 cc per hour, which is the usual augmentation limit according to our data In this subject they found the blood clearance somewhat lower with urine volumes below 50 cc per hour than with volumes above 64 cc per hour Since no regular quantitative relationship between excretion and urine volume was demonstrable from their data, however, these authors concluded that the increase in urea excretion with increase in urine volume, observed over the lower volume ranges by themselves and by Austin, Stillman, and Van Slyke, was due merely to the fact that certain factors stimulated both water and urea excretion the excretion rates of these two substances Addis and Drury conceived to be independent of each other

As opinions still are divided we have considered it desirable to increase the number of observations covering the influence of urine volume on urea excretion in normal subjects We have attempted to limit the factors influencing excretion as nearly as practicable to one, water In some of the experiments data were also obtained on the effect of urea ingestion, which, however, was not observed to affect significantly the clearance values obtained

EXPERIMENTAL

We have examined 5 normal persons between 20 and 30 years of age, all in good health and without any history of kidney disease We also have reexamined another normal subject, now 44 years of age, (Van Slyke), on whom data were first published by Austin, Stillman, and Van Slyke, six years ago

During each experiment (except those on Van Slyke) the person examined was kept in bed The reasons for this were, first, that changes of position are said to influence the water excretion through the kidneys (White, Rosen, Fischer and Wood (1926)) and, second, that the kidney function of patients is nearly always examined while they are in bed, so it seems more correct to compare them with normals studied under similar conditions

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urea concentration was estimated on samples of 3 cc with the aeration urease method of Van Slyke and Cullen (1914)

RESULTS AND DISCUSSION

The conditions and results of all our experiments are given in tables 1 to 4

The results for each of the 6 subjects investigated by us, and for one other from the literature (Rehberg, 1926), have been plotted in figures 3 to 9 with clearance values as ordinates and $\sqrt{V}$ as abscissae In order to simplify the plotting by obtaining straight line curves we have laid off as abscissae values of the square root of the urine volume According to the square root rule, this procedure should enable one to express the relationship between urine volume and blood clearance as a rising straight line below the augmentation limit, and it will be seen in the graphs that such is the case Above the augmentation limit volume has no effect, and the excretion curve becomes a horizontal line

The curves have been drawn in the following manner The mean value of the clearance $\frac{UV}{B}$, in cubic centimeters of blood containing the amount of urea excreted per minute, for all points above the augmentation limit is taken, and at the corresponding height above the horizontal axis, and parallel to it, a line is drawn Then for all points to the left of the augmentation limit the standard clearance $\frac{U}{B}\sqrt{V}$ is calculated, and the mean value is taken This average determines the height of the curve at $V = 1$ cc Through the corresponding point on the vertical line representing $V = 1$ cc, and through the zero point, a straight line is drawn The position of the augmentation limit is calculated as the intersection point between this slanting line and the horizontal line first drawn

In this way we have calculated augmentation limits from the data given by Austin, Stillman, and Van Slyke on Austin and Van Slyke our own data on six normal subjects, and finally the data given by Rehberg (1926) on himself, that were collected by him for quite other reasons, but can be used for our purpose as well

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TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_s = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_s = 54$, $C_m = 75$
		cc per minute	*mg per 100 cc*	*mg per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Experiment Number 1	9–10	7 17	415	39 3	75 5*		101*
J F M	10–11	8 08	324	38 5	68 0*		91*
7 a m , 30 grams urea and	11–12	4 00	842	46 6	72 3*		96*
500 cc. of water 10 and	12–1	2 42	1321	44 9	71 2*		95*
11 a.m., 12 noon and 1	1–2	1 63	1398	36 7	62 2	48 6	90
p m., 5 grams, urea each	2–3	1 67	1273	42 5	49 8	38 7	72
time							
Experiment Number 8	9–10	0 75	1568	25 1	46 8	54 1	100
J F M	10–11	0 92	1564	29 0	49 5	51 8	96
7 15 a m , 15 grams urea	11–12	1 08	1260	29 9	45 7	43 8	81
12 45 p m , lunch 1 and	12–1	0 60	1185	24 6	29 0	37 3	69
2 p m , 1000 cc of water	1–2	1 03	1366	24 7	57 2	56 2	104
each time	2–3	8 58	193	21 9	75 7*		101*
Experiment Number 3	9–10	1 67	1068	25 8	69 2	53 5	99
A H	10–11	1 42	1034	25 5	57 5	48 3	89
7 a m , 15 grams urea 11	11–12	3 67	593	32 3	67 3*		90*
a m , 20 grams urea and	12–1	7 87	264	40 0	52 2*		70*
200 cc of water 1 30	1–2	2 08	1095	34 2	67 0	46 2	85
p m , lunch and 200 cc of	2–3	2 42	901	31 7	68 8*		92*
water							
Experiment Number 25	9–10	0 57	679	13 5	28 5	37 9	70
A H	10–11	0 57	747	13 2	32 0	42 7	79
8 30, breakfast. 12 noon,	11–12	0 63	800	12 6	40 2	50 4	93
lunch and 1000 cc of	12–1	1 63	495	13 3	60 8	47 5	88
water 1 p.m., 500 cc of	1–2	10 83	87 3	13 6	77 5*		103*
water	2–3	9 07	88 8	13 1	61 5*		82*
Experiment Number 5	10–11	0 60	1074	15 6	41 3	53 3	99
W N							
7 a m , breakfast and 15							
grams urea in 75 cc. of							
water Could not void							
on time							

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_s = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_s = 54$, $C_m = 75$
		cc per minute	*mg per 100 cc*	*mg per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Experiment Number 1	9–10	7 17	415	39 3	75 5*		101*
J F M	10–11	8 08	324	38 5	68 0*		91*
7 a m , 30 grams urea and	11–12	4 00	842	46 6	72 3*		96*
500 cc. of water 10 and	12–1	2 42	1321	44 9	71 2*		95*
11 a.m., 12 noon and 1	1–2	1 63	1398	36 7	62 2	48 6	90
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200 cc of water 1 30	1–2	2 08	1095	34 2	67 0	46 2	85
p m , lunch and 200 cc of water	2–3	2 42	901	31 7	68 8*		92*
Experiment Number 25	9–10	0 57	679	13 5	28 5	37 9	70
A H	10–11	0 57	747	13 2	32 0	42 7	79
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lunch and 1000 cc of	12–1	1 63	495	13 3	60 8	47 5	88
water 1 p.m., 500 cc of	1–2	10 83	87 3	13 6	77 5*		103*
water	2–3	9 07	88 8	13 1	61 5*		82*
Experiment Number 5	10–11	0 60	1074	15 6	41 3	53 3	99
W N							
7 a m , breakfast and 15 grams urea in 75 cc. of water Could not void on time							

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_s = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_s = 54$, $C_m = 75$
		cc per minute	*mg per 100 cc*	*mg per 100 cc*	*cc. blood per minute*	*cc per blood minute*	*per cent*
Experiment Number 28	9–10	0 97	781	19 4	38 8	39 6	73
J C B	10–11	1 00	731	19 2	38 1	38 1	71
7 30 a.m , breakfast. 12	11–12	1 25	656	18 9	43 3	38 8	72
noon, lunch	12–1	1 02	642	16 6	39 3	39 1	72
	1–2	0 80	746	17 2	34 7	38 8	72
Experiment Number 31	9–10	7 33	119 4	14 7	59 6*		79*
J C B	10–11	7 58	103 3	12 5	62 6*		83*
7 30 a.m , breakfast and 500	11–12	8 75	83 4	12 3	59 3*		79*
cc. of water 8 40, 10, 11	12–1	6 67	113 7	11 3	67 2*		90*
a m , and 12 noon, 500	1–2	12 33	54 2	11 2	59 6*		79*
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noon, lunch 1 p m., 300							
cc and 2 p m , 200 cc of							
water							
Experiment Number 33	10–11	0 80	765	13 7	44 6	49 8	92
D V S , 1927	11–12	1 33	640	11 6	73 6	63 6	118
8 30, breakfast 12 45	12–1	1 07	619	12 7	52 0	50 3	93
p m , lunch No fluids	1–2	0 73	775	11 2	50 7	59 2	110
Cutaneous blood	2–3	0 50	906	10 3	44 0	62 2	115
	3–4	0 70	806	9 4	60 0	71 7	133
	4–5	0 60	808	(9 4)	51 6	66 5	123
Experiment Number 34	9–10	6 41	153	13 1	74 8*		100*
D V S 1927	10–11	16 25	58 6	12 3	77 4*		103*
8 30 a m , breakfast with	11–12	13 25	86 0	12 3	92 6*		123*
800 cc. of water 8 50	12–1	6 37	137	10 3	84 8*		113*
and 9 15 a m 200 cc.,	1–2	5 26	173	9 6	94 8*		126*
9 20 400 cc , 9 35 10 cc ,	2–3	1 32	438		60 2	52 4	97
and 10 40 200 cc., 10 45	3–4	2 77	281	(9 0)	86 4*		115*
400 cc. of water 12 30							
p m , lunch with 200 cc.							
of water Venous blood							

TABLE 2—*Continued*

Experiments	Time	V Urine volume	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV}{B}$ Observed clearance*	$C_s = \frac{U\sqrt{V}}{B}$ Standard clearance, calculated for $V = 1$, from observed clearances below augmentation limits	Per cent of average normal clearance, taken as $C_s = 54$, $C_m = 75$
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and 10 40 200 cc., 10 45	3–4	2 77	281	(9 0)	86 4*		115*
400 cc. of water 12 30 p m, lunch with 200 cc. of water Venous blood							

The results of these calculations are given in table 4

In addition to the above experiments, in which the complete excretion curves were obtained over the maximum urine volume range, observations with ordinary urine volumes, below the augmentation limit, were made on 9 other normal subjects, and are reported, with the resulting standard clearance values, in table 3 The subjects were young men engaged in such activity as involves ordinary laboratory work

The augmentation limit It is seen from table 4, that the augmentation limit in the 8 normal subjects observed occurs at between 1 67 and 2 55 cc per minute, if the observation made on Van Slyke in 1921 is excluded The higher augmentation limit in this case, due to a very high average maximum clearance, falls statistically outside the group, since it differs by more than four times the mean error[3] from the average There were only 4 determinations with high urine volumes in this case (data of Austin, Stillman, and Van Slyke) and they were made while the subject was about the laboratory, and not under the conditons of rest imposed on the subjects used for the analyses reported n this paper Accordingly additional experiments on the same subject have been performed with the present series of observations, during which the subject was sitting quietly at his desk The augmentation limit and clearances thus obtained fall within the limits of the rest of our observations In the calculation of the average augmentation limit and maximum clearance, and the variation for the group of normal subjects, given in tables 3 and 4, only the present figures are used for this subject

NORMAL VALUES AND VARIATIONS OF THE STANDARD AND MAXIMUM BLOOD UREA CLEARANCES

In table 4 are summarized the mean standard clearances of the normal subjects reported in detail in tables 2 and 3, and in addition the standard clearances calculated from previous data of Austin, Stillman and Van Slyke (1921) Similarly in table 5 are summarized

[3] The mean error calculated as the standard deviation, $\pm\sqrt{\dfrac{\Sigma - a^2}{n-1}}$, divided by the square root of the number of observations (fig 9)

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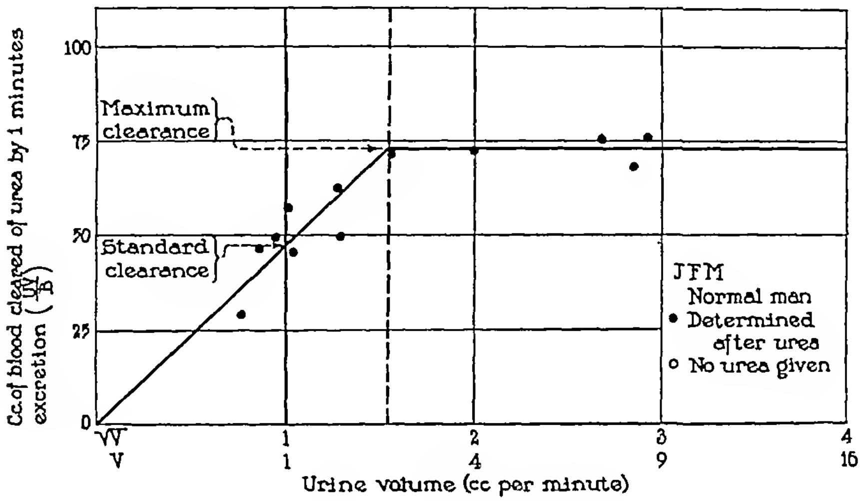

FIG 3 UREA EXCRETION CURVE FROM NORMAL SUBJECT

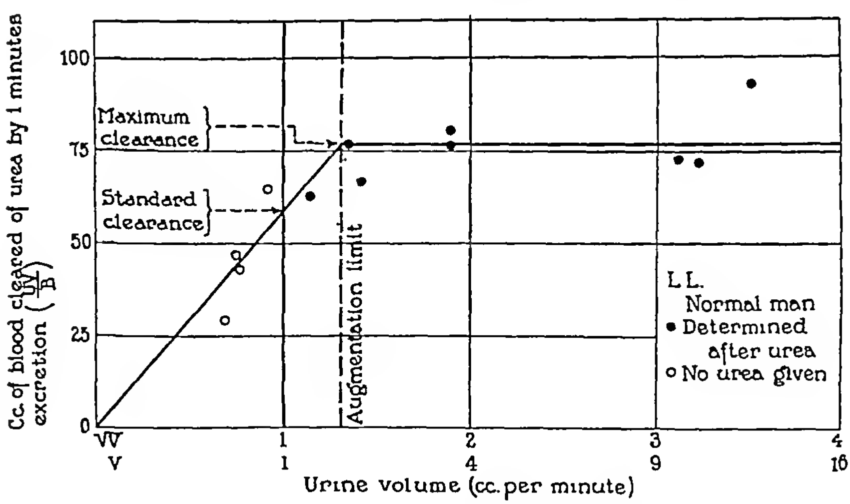

FIG 4 UREA EXCRETION CURVE FROM NORMAL SUBJECT

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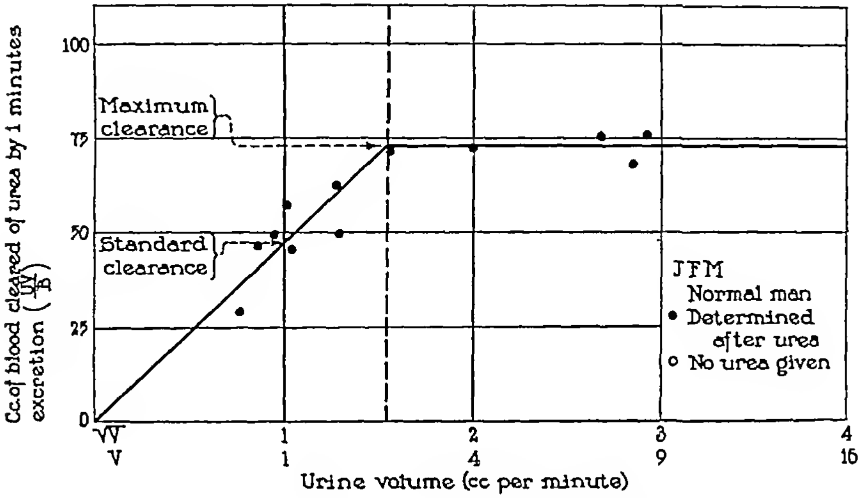
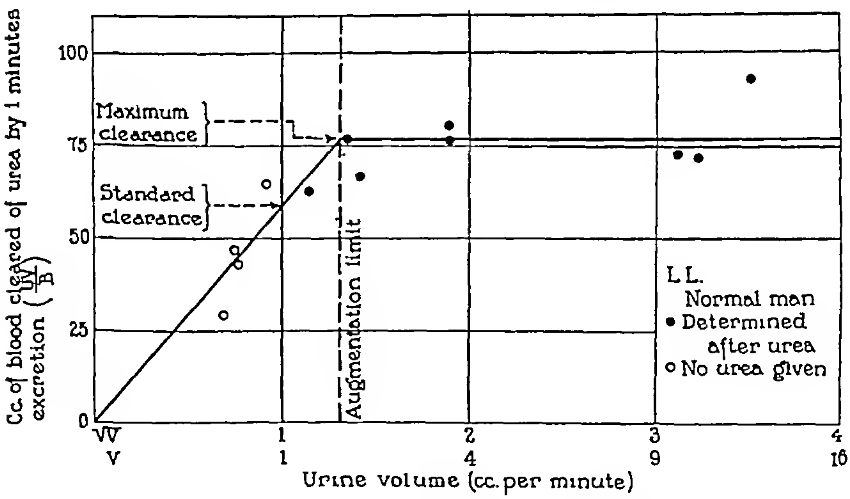


FIG 3 UREA EXCRETION CURVE FROM NORMAL SUBJECT



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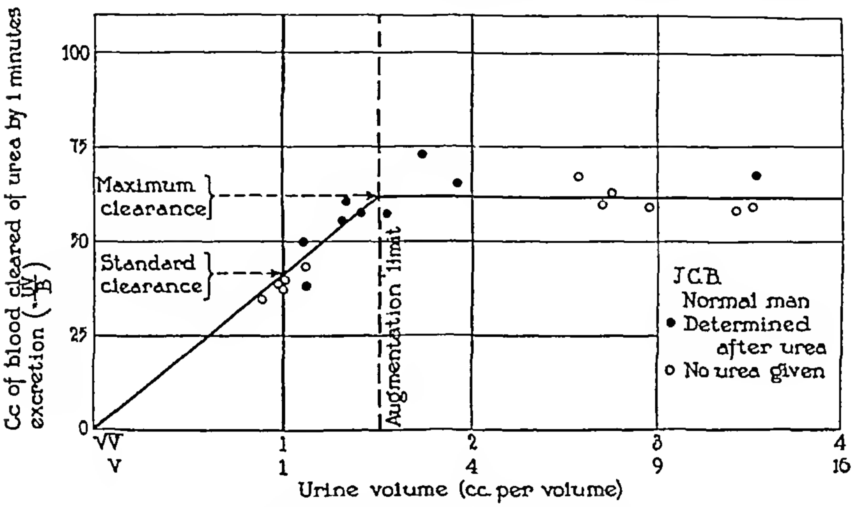

FIG 7 UREA EXCRETION CURVE FROM NORMAL SUBJECT

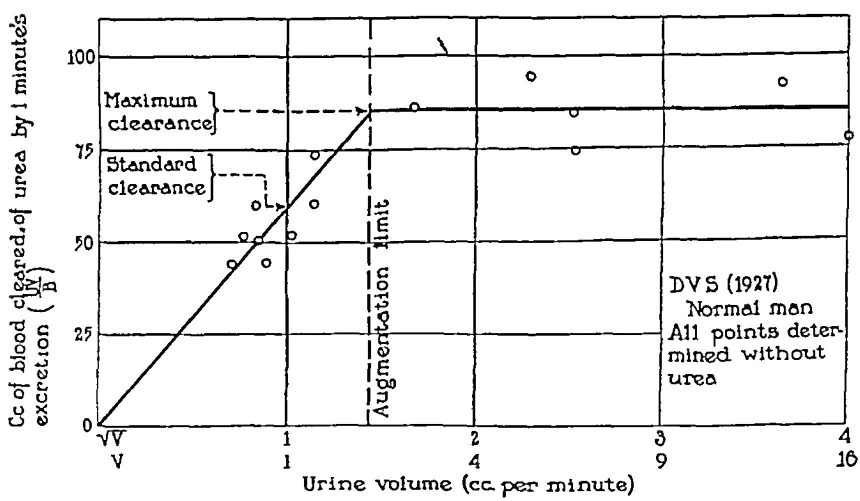

FIG 8 UREA EXCRETION CURVE FROM NORMAL SUBJECT

The results of our experiments, plotted in figures 3 to 8, and those calculated from the data of Rehberg, plotted in figure 9, confirm the conclusions of Austin, Stillman, and Van Slyke There is a distinct

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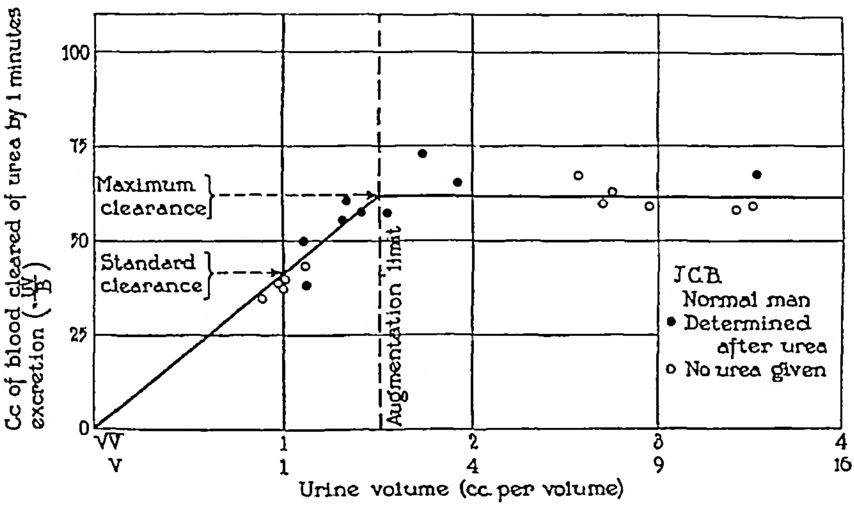

Fig 7 Urea Excretion Curve from Normal Subject

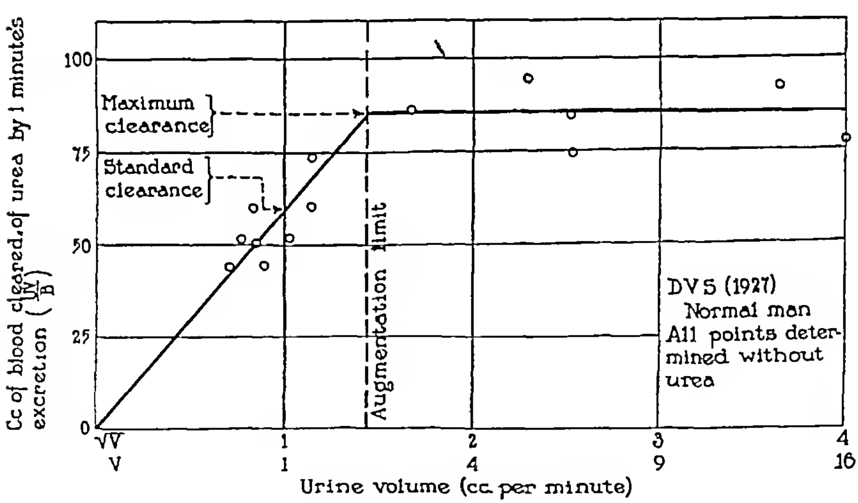

Fig 8 Urea Excretion Curve from Normal Subject

The results of our experiments, plotted in figures 3 to 8, and those calculated from the data of Rehberg, plotted in figure 9, confirm the conclusions of Austin, Stillman, and Van Slyke There is a distinct

augmentation limit Below it the clearance increases with increasing urine volume, while above it the clearance is independant of urine volume The grouping of points about the slanting portion of the curve indicates that the square-root rule which this portion represents expresses the average effect of urine volume changes No other line or curve could follow the experimental points more closely The deviations of the points are frequently considerable, since other, unknown factors, besides urine volume influence the rate of urea excretion (Addis and Drury, 1923) It is obvious, however, that the

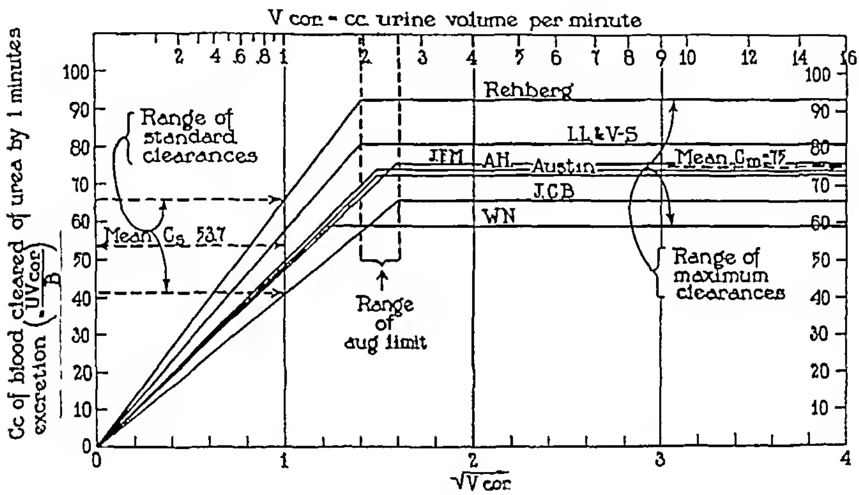

Fig 11

Same curves as in Figure 10, but corrected for body size by multiplying V values by the correction factor $\dfrac{1\ 73}{\text{square meters surface area}}$

square-root rule is followed with sufficient constancy to make interpretations of urea excretion rates with ordinary urine volumes (below the augmentation limit) much more exact when corrected for the volume effect than they would be if urine volume as a factor were neglected In fact, the deviations of the experimental points from the slanting line representing this rule are not significantly greater than the deviations from the horizontal part of the curves covering ranges in which urine volume changes do not influence output The square-root rule affords as satisfactory a correction for urine volume

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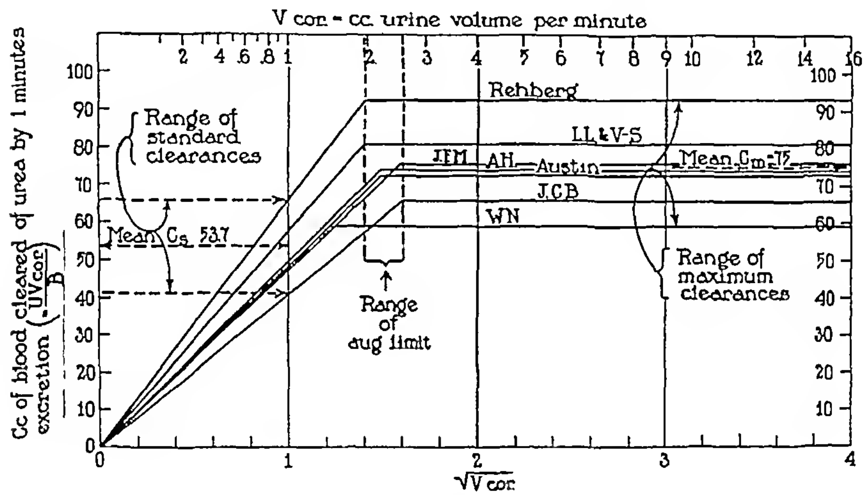

FIG 11

Same curves as in Figure 10, but corrected for body size by multiplying V values by the correction factor $\frac{1.73}{\text{square meters surface area}}$

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1 Increase in urine volume diminishes the amount of work the kidney has to do against osmotic pressure in compressing each gram of urea from the volume it occupies in the blood to the smaller volume it occupies in the urine Less work is required to compress the urea of 100 cc of blood into 2 cc of urine than to compress it further into 1 cc of urine The kidneys, because they work more easily with increased urine volume, may work faster, and excrete more urea per minute From this view point, the increase in urea excretion rate which accompanies accelerated water output is a direct cause of the latter (For quantitative calculation according to the laws of thermodynamics of the mechanical work done by the kidney per gram molecule of substance excreted see pages 93 to 96 of Barcroft (1914))

2 The other hypothesis is that increase of renal circulation, or stimulus of the secretory activity of the renal cells, may accelerate excretion of both urea and water The accelerated water output in this case would not be the cause of the accelerated urea output Both would be due to a common stimulus acting on the kidney Even dilution of the blood by water drinking might be such a cause, either inducing larger proportions of renal capillaries to open up (*vide* Richards (1920–21)) or, making the secretory cells become more active

For the purpose of estimating from urea excretion the work which the kidneys will do under standard conditions it is, however, a matter of indifference whether the acceleration of urea output that comes with increased urine volume is caused by the latter, or merely accompanies it as the result of a renal stimulus that affects both Whether, in introducing $\sqrt{V}$ as a factor in the standard blood urea clearance calculation, we are dealing with the direct cause of fluctuations of clearance with urine volume, or are using urine volume as a fairly consistent indicator of such cause, does not greatly matter when we are concerned merely with measurement of renal ability

SUMMARY

1 The relationship between urine volume and urea excretion has been studied in 6 more normal adults

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clearance C_s, and maximum blood urea clearance C_m, defined in the preceding paper (6), are accordingly written as

$$C_s = \frac{U}{B}\sqrt{V \times \frac{1.73}{A}} = \frac{U}{B}\sqrt{V_{cor}}$$

$$C_m = \frac{U}{B} \times V \times \frac{1.73}{A} = \frac{U \times V_{cor}}{B}$$

The corrected urine volume, V_{cor}, is the observed volume of urine in cubic centimeter per minute multiplied by the factor $\frac{1.73}{A}$, A being the body area in square meters that is normal for the subject's height and age. The clearance formulae, written with V_{cor} in place of V, indicate the cubic centimeters of blood per *unit surface area* cleared of urea per minute, the unit of surface urea being 1.73 square meters. In the case of the C_s formula, with V_{cor}, the value calculated indicates the cubic centimeters blood clearance per unit surface area when the per minute urine volume is 1 cc. per unit surface area. Blood clearance, urine volume, and hence augmentation limit are thus all based on surface area. (See derivation of original formula on page 102 of Austin, Stillman and Van Slyke (1).)

The *correction for body size* is applied as follows. The age and height of the subject having been ascertained, the value of the correction factor $\frac{1.73}{A}$ is read from the line chart in figure 1. The observed value of V, in cubic centimeters of urine per minute, is multiplied by this factor. The corrected V thus obtained is used in the standard clearance formula, $C_s = \frac{U\sqrt{V_{cor}}}{B}$, or the maximum clearance formula, $C_m = \frac{UV_{cor}}{B}$, for the calculations outlined in the preceding paper (6).

In the correction factor $\frac{1.73}{A}$, A represents in square meters the mean surface area of normal persons of the subject's height and age. Surface area is thus used as the nearest available parallel to the mass of functioning renal tissue (8) present in a normal subject. Because of the likelihood that the subjects examined will be obese, edematous, or

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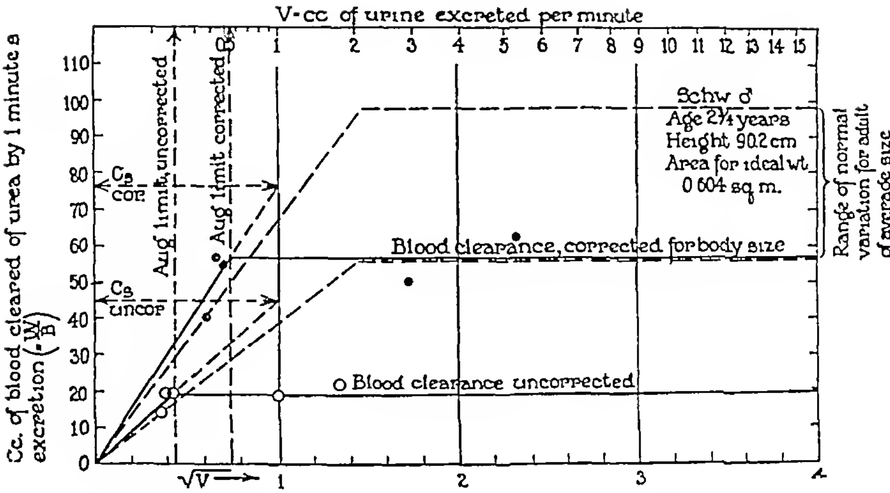


FIG 2 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 13 6 KGM IDEAL WEIGHT

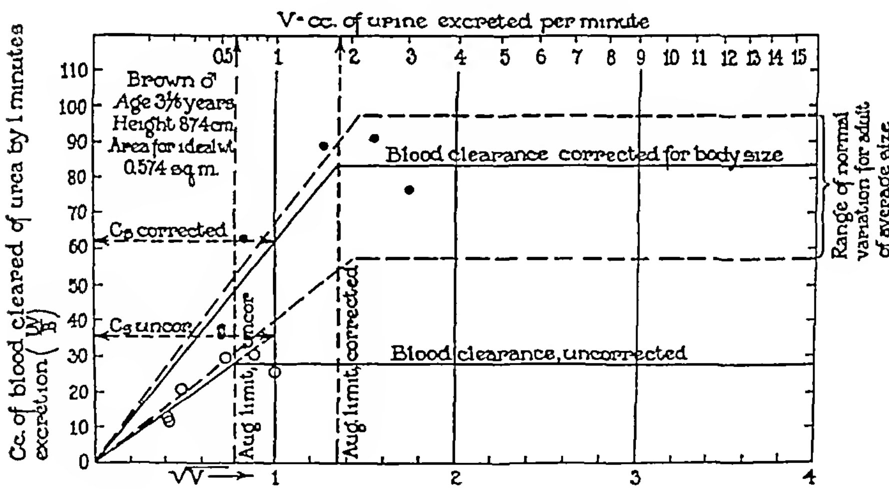
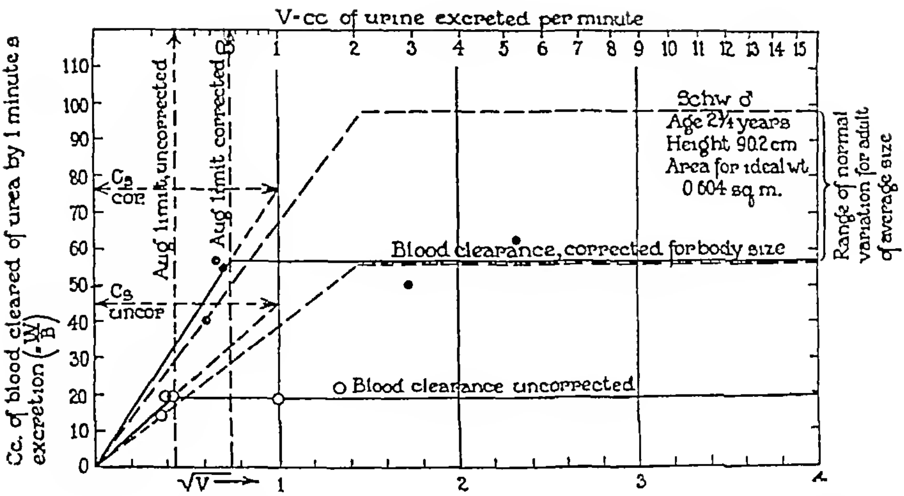


FIG 3 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 12 6 KGM IDEAL WEIGHT



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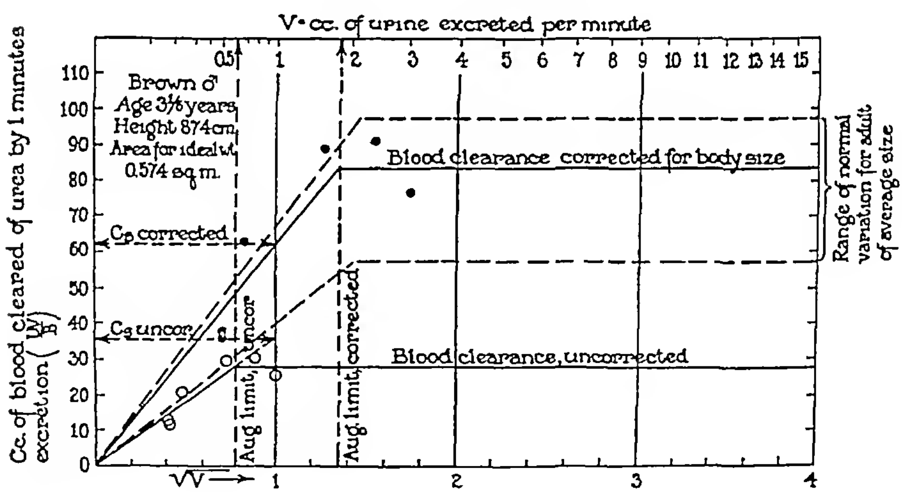

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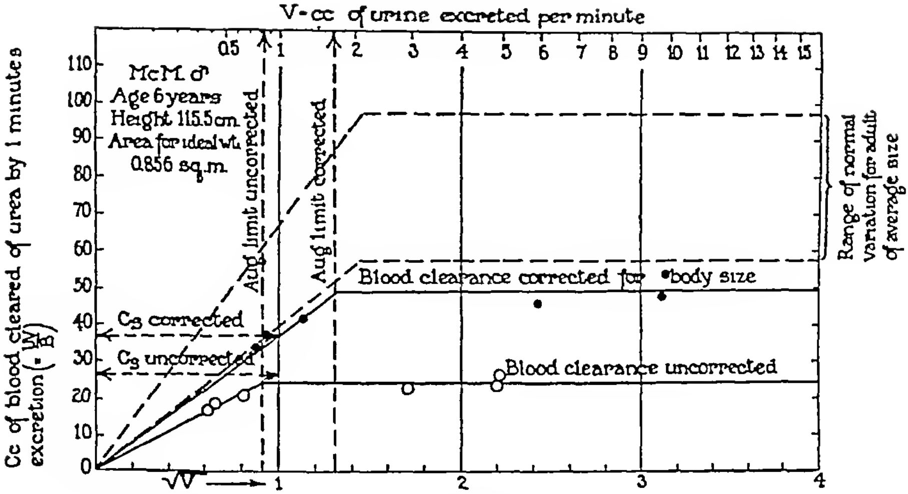


FIG 6 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 21 1 KGM IDEAL WEIGHT

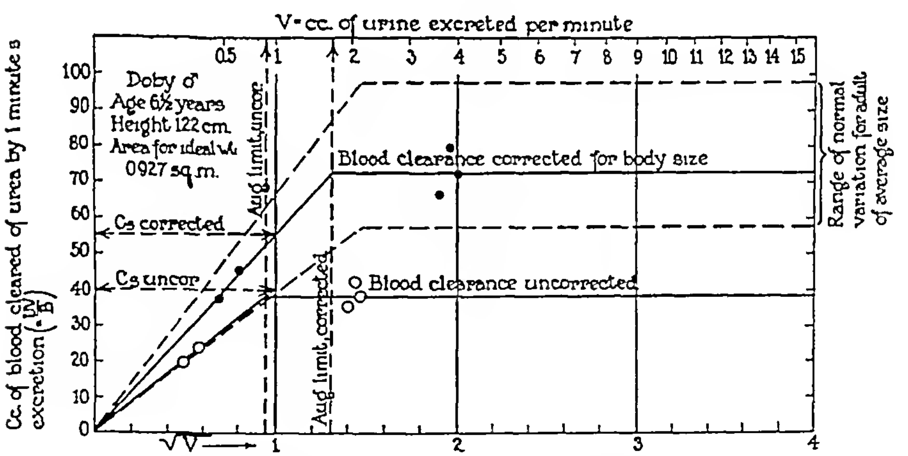
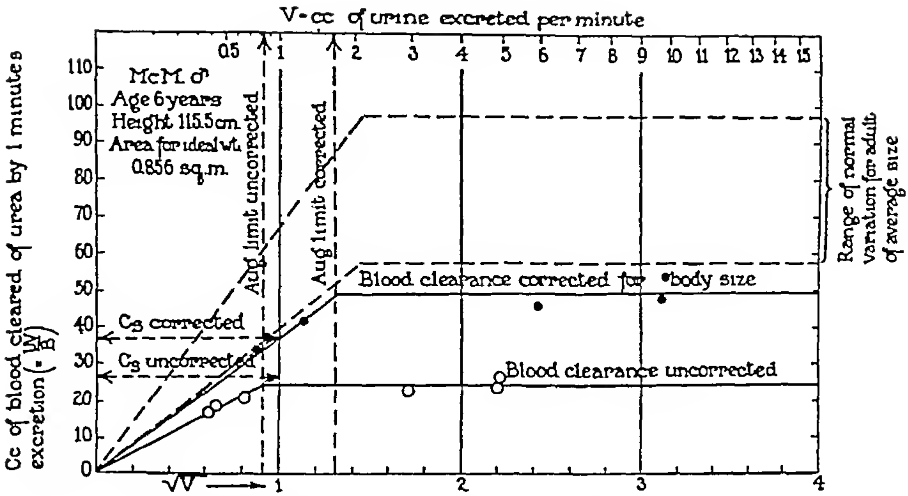


FIG 7 UREA EXCRETION CURVE, UNCORRECTED AND CORRECTED FOR SURFACE AREA, OF CHILD OF 23 8 KGM IDEAL WEIGHT



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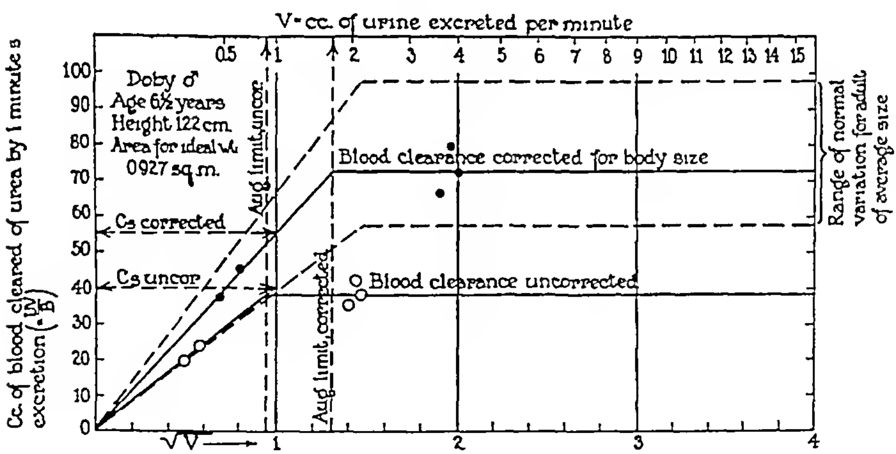

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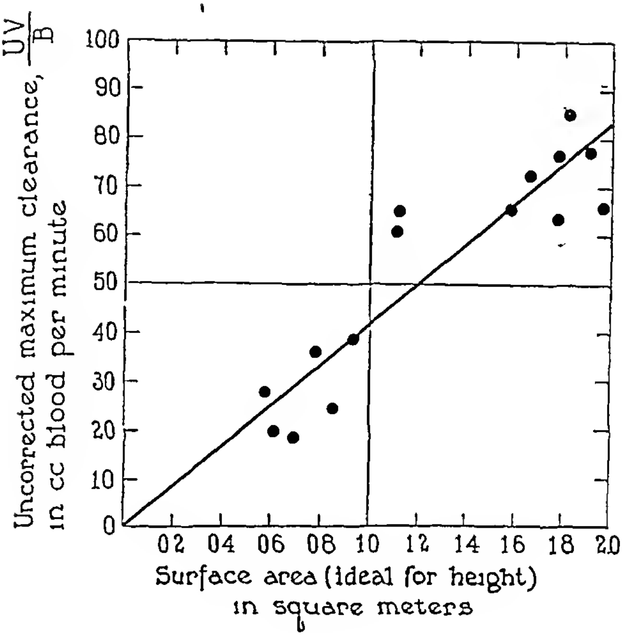

Fig 10 Relationship of Surface Area to Uncorrected Maximum Clearance Values of Normal Adults and Children

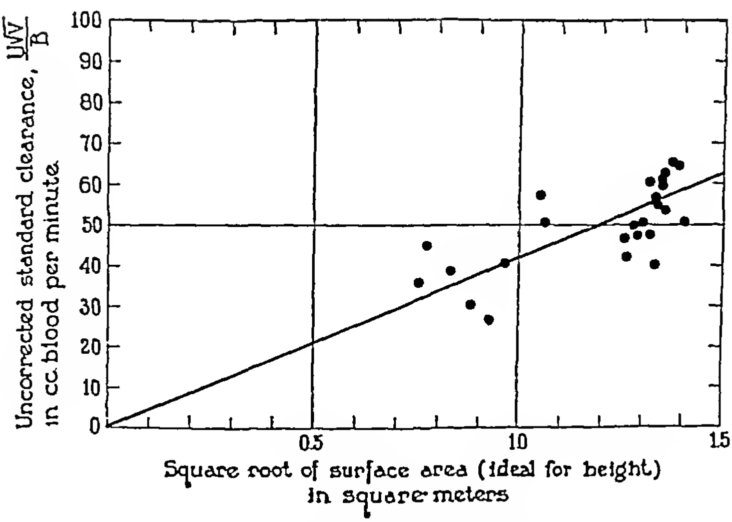

Fig 11 Relationship of Surface Area to Uncorrected Standard Clearance Values of Normal Adults and Children

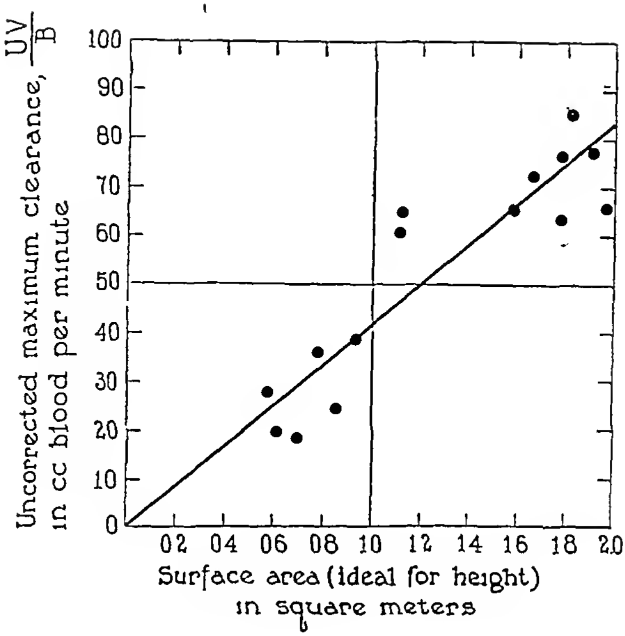

FIG 10 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED MAXIMUM CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

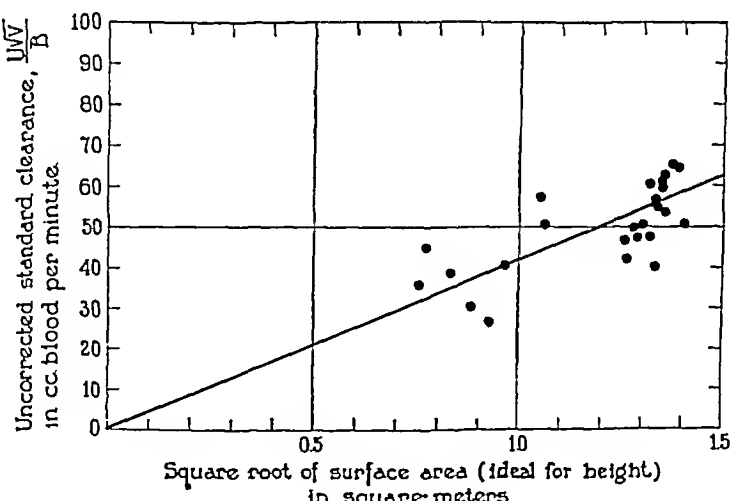

FIG 11 RELATIONSHIP OF SURFACE AREA TO UNCORRECTED STANDARD CLEARANCE VALUES OF NORMAL ADULTS AND CHILDREN

TABLE 1

Data concerning urea excretion

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1.73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1.73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1.73}{A} = 1$ from observations below augmentation limit
	mgm per 100 cc	*mgm per 100 cc*	*cc per minute*	*cc per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*
Schw ♂	1,121	(10.5)	0.132	0.370	14.1	38.8	39.5	64.9
2 $\frac{9}{12}$ years	1,346	10.5	0.154	0.431	19.8	50.4	55.3	84.2
15.9 kgm	1,147	10.5	0.176	0.493	19.2	45.8	53.8	76.5
90.2 cm height	260	15.1	1.03	0.287	17.7*		49.4*	
0.620 sq m surface area ideal for height	175	(15.0)	1.88	0.529	21.9*		61.7*	
$\frac{1.73}{\text{Area}} = 2.80$	Average clearance				19.8*	45.0	55.5*	75.2
Brown ♂	832	11.0	0.167	0.486	12.6	30.9	36.7	52.6
3 $\frac{2}{12}$ years	756	(10.6)	0.167	0.486	11.9	29.2	34.7	49.7
14.6 kgm	912	10.2	0.233	0.677	20.8	43.2	60.6	73.5
87.4 cm height	527	9.5	0.534	1.55	29.5	40.4	86.0	69.0
0.595 sq m surface area	337	8.9	0.793	2.4	30.2*		90.8*	
ideal for height	235	(9.20)	1.000	2.91	25.5*		74.4*	
$\frac{1.73}{\text{Area}} = 2.91$	Average clearance				27.9*	35.9	82.6*	61.2

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Data concerning urea excretion

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1\ 73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1\ 73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1\ 73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1\ 73}{A} = 1$ from observations below augmentation limit
	mgm per 100 cc	*mgm per 100 cc*	*cc per minute*	*cc per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*
Schw ♂	1,121	(10 5)	0 132	0 370	14 1	38 8	39 5	64 9
2 $\frac{9}{12}$ years	1,346	10 5	0 154	0 431	19 8	50 4	55 3	84 2
15 9 kgm	1,147	10 5	0 176	0 493	19 2	45 8	53 8	76 5
90 2 cm height	260	15 1	1 03	0 287	17 7*		49 4*	
0 620 sq m surface area ideal for height	175	(15 0)	1 88	0 529	21 9*		61 7*	
$\frac{1\ 73}{\text{Area}} = 2\ 80$	Average clearance				19 8*	45 0	55 5*	75 2
Brown ♂	832	11 0	0 167	0 486	12 6	30 9	36 7	52 6
3 $\frac{9}{12}$ years	756	(10 6)	0 167	0 486	11 9	29 2	34 7	49 7
14 6 kgm	912	10 2	0 233	0 677	20 8	43 2	60 6	73 5
87 4 cm height	527	9 5	0 534	1 55	29 5	40 4	86 0	69 0
0 595 sq m surface area ideal for height	337	8 9	0 793	2 4	30 2*		90 8*	
	235	(9 20)	1 000	2 91	25 5*		74 4*	
$\frac{1\ 73}{\text{Area}} = 2\ 91$	Average clearance				27 9*	35 9	82 6*	61 2

TABLE 1—*Continued*

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1.73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1.73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1.73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1.73}{A} = 1$ from observations below augmentation limit
	mgm per 100 cc	*mgm per 100 cc*	*cc per minute*	*cc per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*
Doty ♂	1,435	18.0	0.250	0.467	19.9	39.9	37.2	54.5
6 $\frac{9}{12}$ years	1,270	17.9	0.343	0.640	24.3	41.6	45.4	56.8
21.3 kgm	307	17.0	1.97	3.68	35.6*		66.5*	
122.0 cm height	281	13.8	2.08	3.88	42.4*		79.2*	
0.927 sq m surface area ideal for height	303	17.0	2.17	4.05	38.7*		72.3*	
$\frac{1.73}{\text{Area}} = 1.87$	Average clearance				38.9*	40.8	72.7*	55.7
Gann ♀	937	(13.2)	0.486	0.751	34.5	49.5	53.3	61.6
9 years	1,115	13.2	0.548	0.846	46.3	62.6	71.5	77.8
26.8 kgm	653	11.7	0.594	0.918	33.2	43.0	51.3	53.5
137 cm height.	466	9.4	0.833	1.29	41.3	45.2	63.8	56.2
1.12 sq m surface area ideal for height	488	8.2	0.933	1.44	55.5	57.5	85.8	71.5
$\frac{1.73}{\text{Area}} = 1.55$	453	8.8	1.07	1.65	54.9	53.2	84.8	66.2
	435	9.2	1.07	1.65	50.4	48.9	77.8	60.8
	479	11.9	1.08	1.67	43.6	41.8	67.4	52.0
	273	14.0	3.40	5.25	66.3*		102.5*	
	197	14.5	4.69	7.24	63.8*		98.6*	
	Average clearance.				65.1*	50.2	100.6*	62.5

TABLE 1—*Continued*

Subject	U Urine urea nitrogen	B Blood urea nitrogen	V Urine volume	$V \times \frac{1\ 73}{\text{Area}}$ Urine volume corrected for body size	Uncorrected clearances: $\frac{UV}{B}$ Observed clearance*	Uncorrected clearances: $\frac{U\sqrt{V}}{B}$ Standard clearance calculated for $V = 1$ from observations below augmentation limit	Clearances corrected for body size: $\frac{U\left(V \times \frac{1\ 73}{A}\right)}{B}$ Observed clearance*	Clearances corrected for body size: $\frac{U\sqrt{V \times \frac{1\ 73}{A}}}{B}$ Standard clearance calculated for $V \times \frac{1\ 73}{A} = 1$ from observations below augmentation limit
	mgm per 100 cc	*mgm per 100 cc*	*cc per minute*	*cc per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*
Doty ♂	1,435	18 0	0 250	0 467	19 9	39 9	37 2	54 5
6 $\frac{9}{12}$ years	1,270	17 9	0 343	0 640	24 3	41 6	45 4	56 8
21 3 kgm	307	17 0	1 97	3 68	35 6*		66 5*	
122 0 cm height	281	13 8	2 08	3 88	42 4*		79 2*	
0 927 sq m surface area ideal for height	303	17 0	2 17	4 05	38 7*		72 3*	
$\frac{1\ 73}{\text{Area}} = 1\ 87$	Average clearance				38 9*	40 8	72 7*	55 7
Gann ♀	937	(13 2)	0 486	0 751	34 5	49 5	53 3	61 6
9 years	1,115	13 2	0 548	0 846	46 3	62 6	71 5	77 8
26 8 kgm	653	11 7	0 594	0 918	33 2	43 0	51 3	53 5
137 cm height.	466	9 4	0 833	1 29	41 3	45 2	63 8	56 2
1 12 sq m surface area ideal for height	488	8 2	0 933	1 44	55 5	57 5	85 8	71 5
$\frac{1\ 73}{\text{Area}} = 1\ 55$	453	8 8	1 07	1 65	54 9	53 2	84 8	66 2
	435	9 2	1 07	1 65	50 4	48 9	77 8	60 8
	479	11 9	1 08	1 67	43 6	41 8	67 4	52 0
	273	14 0	3 40	5 25	66 3*		102 5*	
	197	14 5	4 69	7 24	63 8*		98 6*	
	Average clearance.				65 1*	50 2	100 6*	62 5

In estimating the maximum blood urea clearance, however, by the formula $C_m = \frac{UV}{B}$, a 10 per cent correction to V causes a 10 per cent correction to the C_m value calculated Hence, to avoid an error greater than ±5 per cent, we can neglect body size in estimating the maximum clearance only in adults between 164 and 176 cm , or 65 and 69 inches, in height

EXPERIMENTAL

In order to measure satisfactorily the influence of body size on urea excretion rate it is necessary to compare children with adults With ordinary adults variation in size, as a factor in influencing the volume of blood, the urea content of which is excreted per minute, is less important than other, unknown factors, which may be summarized as "individual constitution" These may cause the standard or maximum clearance of an individual, of average size and normal to all appearances, to vary by as much as 25 per cent from the mean normal clearance The effect of body size is so obscured by the greater effects of individual constitution that the size effect in adults can be measured only by statistical methods In order to make it an outstanding factor it is necessary to study subjects with a greater size range than can be obtained in the adults usually available for observation

We have accordingly, by the technique described in the preceding paper (6), determined the urea excretion curves on a number of children The numerical data are given in table 1, and the curves in figures 2 to 9 The correction for body size is made, as previously described, by multiplying the observed V value by the factor $\frac{1.73}{A}$

DISCUSSION OF RESULTS

It is obvious from figures 2, 3, 4, 5, 6, 7, 8, and 9, that correcting the blood urea clearances, by multiplying the observed values of V in cc urine excreted per minute by the factor $\frac{\text{average adult surface area}}{\text{surface area of subject}} = \frac{1.73}{A}$, causes data from children, at least down to 3 years of age, to fall

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jects do not decrease so rapidly as body weights They decrease rather as the surface area, or the 2/3 power of the weight

The degree of exactness with which the maximum clearance, $\frac{UV}{B}$, varies in proportion to surface area in different subjects is indicated by figure 10 in which we have plotted against surface area the mean maximum clearance for each of the 7 adults reported from this laboratory in the preceding paper (6), and each of the children reported in the present paper In figure 11 the uncorrected standard clearance, $\frac{U\sqrt{V}}{B}$, is similarly plotted against the square root of surface area for each of the 17 adults reported in the preceding paper, and each of the children in the present one

SUMMARY

The calculated maximum and standard blood urea clearances, previously defined (6), may be corrected for variations in body size by means of a factor based on the assumption, introduced by Addis (8), that excretion varies directly as surface area Thus corrected, data from small children yield the same normal values as adults for the maximum and standard clearances, and also for the augmentation limit of urine volume, at which maximum excretory efficiency is attained

The nature of the standard clearance formula is such that correction for body size in persons between 62 and 71 inches in height does not exceed 5 per cent, and in tests of renal function may be neglected

For the maximum clearance the range of height with less than 5 per cent correction is 65 to 69 inches

BIBLIOGRAPHY

1 Austin, J H, Stillman, E, and Van Slyke, D D, J Biol Chem, 1921, xlvi, 91 Factors Governing the Excretion Rate of Urea

2 Benedict, F G, and Talbot, F B, Publications of Carnegie Institute of Washington, 1921, No 302 Metabolism and Growth from Birth to Puberty

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TABLE 1

Data of cases

Case	Blood pressure	Size of heart	Eye grounds	Hemoglobin as O_2 capacity	Red blood corpuscles	White blood corpuscles	Plasma proteins: Albumin	Plasma proteins: Globulin	Plasma proteins: Total protein	Plasma proteins: A/G ratio	Blood urea	Plasma creatinine	Plasma non protein N	Urine protein (Esbach)	Diuresis (ca)	Specific gravity	Sediment	Phenolsulfonephthalein test in two hours	Mean standard blood $\frac{U}{B}\sqrt{V}$ urea, clearance corrected to body size
				vol umes per cent	*mil lions per cu mm*	*per cu mm*	*per cent*	*per cent*	*per cent*		*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*grams per liter*	*cc*			*per cent*	
1 Chi Hospital No 5335	100/70	Normal	Nor mal	13 2	4 98	5 500	3 34	2 32	5 66	1 44	15	1 3	34	0 3	1 000	1013–1017	+++ RBC, + hyaline and granular casts, no DRG*	70	62
2 Jac. Hospital No 5699	134/85	Slightly in creased	Nor mal	20 2	5 31	6 100	1 71	2 11	3 82	0 81	20	1 9	41	4	1 000	1012–1018	+ RBC, + WBC, +++ hyaline casts, ++ granu lar casts, + DRG		22
3 Cic. Hospital No 5644	115/80	Normal	Nor mal	20 1	4 50	8 900	1 70	2 24	3 94	0 76	22	1 9	29	6	1 200	1010–1014	+ RBC, + WBC, +++ hyaline casts, + granu lar casts, + DRG	35	18
4 Val Hospital No 5446	145/75	Somewhat increased	Nor mal	12 0	4 39	7 300	2 11	1 92	4 03	1 10	40	3 0	32	6	1 600	1010–1018	++ RBC, ++ WBC, ++ RBC casts, ++ granular casts, no DRG		

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				volumes per cent	*millions per cu mm*	*per cu mm*	*per cent*	*per cent*	*per cent*		*mgm per 100 cc*	*mgm per 100 cc*	*mgm per 100 cc*	*grams per liter*	*cc*			*per cent*	
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volumes as low and as high respectively as desired, although many attempts on different days were made This was due to the loss of the power of concentration and of dilution respectively in these two patients

The laboratory findings in our 6 cases of Bright's disease are given in table 1 The terms of classification are those used by Addis (1)

CASE HISTORIES

Case 1 *Chi* Hospital No 5335 Boy, 13 years old When 7 years old he had acute glomerulonephritis, now relapse with hematuria and some edema

TABLE 2

Correction factors for body size

Case			Age	Weight	Height	Body surface area observed	Weight ideal for height and age	Area ideal for height and age	Correction factor	
Name	Number	Hospital number							1 73 / Area observed	1 73 / Area ideal
			years	*kgm*	*cm*	*sq m*	*kgm*	*sq m*		
Chi	1	5335	13	38	145 9	1 30*	37 5	1 29*	1 33	1 34
Jas	2	5699	24	56	173 0	1 66	66 8	1 79	1 04	0 97
Cic	3	5644	24	48	163 4	1 50	59 8	1 65	1 15	1 05
Val	4	5446	24	59	176 0	1 73	69 2	1 84	1 00	0 94
Gia	5	5388	24	64	175 0	1 79	68 3	1 83	0 97	0 95
Wol	6	5731	16	38	155 0	1 31	46 9	1 43	1 32	1 21

* Calculated from the table of Benedict and Talbot for children Carnegie Trust Wash Publ No 302, 1921, p 61

Surface areas of other patients are calculated by Du Bois' formula

No loss of ability to excrete urea or phthalein *Course of the disease* After 6 weeks sent home with no edema, only a trace of albuminuria, and a slight microscopic hematuria Seen 6 months and one year later, when the hematuria had quite disappeared, while the slight albuminuria persisted Other findings normal

Case 2 *Jac* Hospital No 5699 Man, 24 years old One year ago, tonsillitis followed by albuminuria and marked edema This cleared up gradually in 6 months, but after chrysarobin treatment for psoriasis severe relapse set in with edema, ascites and hydrothorax *Course of the disease* Edema and anasarca cleared up completely in one month Seen 6 months later, there was then no edema and only a few red cells and casts in the urine

Case 3 *Cic* Hospital No 5644 Man, 24 years old Syphilis found 6 years ago, since then repeated treatment with salvarsan and mercury One

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TABLE 3

Data concerning urea excretion

	Time	V Urine volume	V cor Urine volume corrected for body size by factor $\frac{1.73}{\text{Area}}$ from table 2	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV \text{ cor}}{B}$ Observed clearance*	$\frac{U\sqrt{V \text{ cor}}}{B}$ Calculated standard below clearance (for V) augmentation limit	Per cent of average normal clearance
		cc per minute	*cc per minute*	*mgm per 100 cc*	*mgm per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Exp No A 12 Chi 8 50 a m, 100 cc of water Venous blood	9–11	0 97	1 30	413	7 5	71 6	62 7	116
Exp No A 13 Chi 8 40 a.m, 100 cc of water Venous blood	9–11	0 67	0 90	678	10 1	60 0	63 6	118
Exp No A 14 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 41	0 55	1019	11 9	96 9	63 4	117
Exp No A 15 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 21	0 28	966	11 1	24 4	46 2	85
Exp No A 16 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 30	0 40	828	7 0	47 6	75 0	139
Exp No A 17 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 28	0 38	1005	10 1	37 4	61 0	113
Exp No A 18 Chi 6 a m, 20 grams urea and 300 cc of water 7, 8, 9, 10, and 11 a m, 300 cc of water each time. Venous blood	9–10 10–11 11–12	6 50 6 92 4 50	8 71 9 27 6 03	282 240 336	30 4 27 0 25 1	80 9* 82 4* 80 7*		108* 110* 108*

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Exp No A 15 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 21	0 28	966	11 1	24 4	46 2	85
Exp No A 16 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 30	0 40	828	7 0	47 6	75 0	139
Exp No A 17 Chi 8 20 a m, 100 cc of water Venous blood	9–11	0 28	0 38	1005	10 1	37 4	61 0	113
Exp No A 18 Chi 6 a m, 20 grams urea and 300 cc of water 7, 8, 9, 10, and 11 a m, 300 cc of water each time. Venous blood	9–10	6 50	8 71	282	30 4	80 9*		108*
	10–11	6 92	9 27	240	27 0	82 4*		110*
	11–12	4 50	6 03	336	25 1	80 7*		108*

TABLE 3—*Continued*

	Time	V Urine volume	V cor Urine volume corrected for body size by factor $\frac{1\ 73}{\text{Area}}$ from table 2	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV \text{ cor}}{B}$ Observed clearance*	$\frac{U\sqrt{V \text{ cor}}}{B}$ Calculated standard below clearance (for V) augmentation limit	Per cent of average normal clearance
		cc per minute	*cc per minute*	*mgm per 100 cc*	*mgm per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Exp 20-a Cic	10–11	0 37	0 39	384	16 2	9 1	14 8	27
9 a m , 100 cc of water Venous blood	11–12	0 60	0 63	386		15 0	19 0	35
Exp 20 b Cic.	10–11	0 50	0 53	347	15 2	11 9	16 6	31
9 a m , 100 cc of water Venous blood	11–12	0 35	0 37	270		6 6	10 8	20
Exp 20 c Cic	10–11	1 27	1 33	198	12 1	21 7	18 9	35
9 a m , 100 cc of water Venous blood	11–12	0 92	0 97	299		23 8	24 3	45
Exp No 22 Cic	9–10	1 92	2 02	354	36 6	19 4*		26*
7 30 a m , breakfast with 15 grams urea	10–11	1 87	1 96	344	35 1	19 2*		26*
and 1000 cc of water 11 50 a m ,	11–12	1 83	1 92	345	34 5	19 2*		26*
lunch with 1000 cc of water 1 20	12–1	2 17	2 28	349	34 6	22 9*		31*
and 2 05 p m , 500 cc of water each	1–2	4 17	4 38	209	37 0	24 7*		33*
time Cutaneous blood	2–3	4 50	4 73	230	35 4	30 7*		41*
	3–4	4 83	5 07	185	33 8	27 8*		37*
Exp No 14 Val	9–10	1 10	1 03	244	21 8	11 6	11 3	21
8 a m , breakfast with 100 cc of water	10–11	0 97	0 91	265	19 4	12 4	13 1	24
12 noon lunch with 1000 cc of water	11–12	0 90	0 85	285	18 9	12 9	13 9	25
1 40 p m , 500 cc of water Cutaneous blood	12–1	2 17	2 04	135	22 1	12 5*		17*
	1–2	5 08	4 78	57	20 5	13 2*		18*
	2–3	6 37	5 99	50	19 6	15 2*		20*
Exp No 14-a Val	10–11	1 87	1 76	222		14 9*		21*
9 a m , 100 cc. of water Venous blood	11–12	0 88	0 83	361	26 1	11 5	12 6	23

TABLE 3—*Continued*

	Time	V Urine volume	V cor Urine volume corrected for body size by factor $\frac{1\ 73}{\text{Area}}$ from table 2	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV \text{ cor}}{B}$ Observed clearance*	$\frac{U\sqrt{V \text{ cor}}}{B}$ Calculated standard below clearance (for V) augmentation limit	Per cent of average normal clearance
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	1–2	5 08	4 78	57	20 5	13 2*		18*
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TABLE 3—*Concluded*

	Time	V Urine volume	V cor Urine volume corrected for body size by factor $\frac{1.73}{\text{Area}}$ from table 2	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV \text{ cor}}{B}$ Observed clearance*	$\frac{U\sqrt{V \text{ cor}}}{B}$ Calculated standard below clearance (for V) augmentation limit	Per cent of average normal clearance
		cc per minute	*cc per minute*	*mgm per 100 cc*	*mgm per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Exp A 24 Gia 8 20 a m, 100 cc of water Venous blood	9–11	1 02	0 97	269	34 8	7 4	7 61	14
Exp A-25 Gia 8 20 a m, 100 cc of water Venous blood	9–11	0 80	0 76	314	35 3	6 8	7 76	14
Exp A 26 Gia 9 05 a m, 100 cc of water Venous blood	9–11	1 04	0 99	339	37 0	9 0	9 10	17
Exp A-27 Gia 8 25 a m, 100 cc of water Venous blood	9–11	0 97	0 92	388	44 6	8 1	8 36	15
Exp A-28 Gia 8 30 a m, 100 cc of water Venous blood	9–11	0 97	0 92	362	39 4	8 4	8 82	16
Exp A 29 Gia 6 a m, 30 grams urea and 500 cc of water 7, 8, 9, 10, and 11 a m, 500 cc of water each time Venous blood	9–10	2 17	2 06	362	71 9	10 3*		14*
	10–11	3 37	3 20	268	70 4	12 2*		16*
	11–12	4 17	3 96	209	69 0	12 1*		16*
Exp A-30 Gia 8 25 a m, 100 cc. of water Venous blood	9–11	1 17	1 11	435	49 9	9 7	9 19	17

TABLE 3—*Concluded*

	Time	V Urine volume	V cor Urine volume corrected for body size by factor $\frac{1\ 73}{\text{Area}}$ from table 2	U Urine urea nitrogen	B Blood urea nitrogen	$\frac{UV\ \text{cor}}{B}$ Observed clearance*	$\frac{U\sqrt{V\ \text{cor}}}{B}$ Calculated standard below clearance (for V) augmentation limit	Per cent of average normal clearance
		cc per minute	*cc per minute*	*mgm per 100 cc*	*mgm per 100 cc*	*cc blood per minute*	*cc blood per minute*	*per cent*
Exp A 24 Gia 8 20 a m , 100 cc of water Venous blood	9–11	1 02	0 97	269	34 8	7 4	7 61	14
Exp A-25 Gia 8 20 a m , 100 cc of water Venous blood	9–11	0 80	0 76	314	35 3	6 8	7 76	14
Exp A 26 Gia 9 05 a m , 100 cc of water Venous blood	9–11	1 04	0 99	339	37 0	9 0	9 10	17
Exp A-27 Gia 8 25 a m , 100 cc of water Venous blood	9–11	0 97	0 92	388	44 6	8 1	8 36	15
Exp A-28 Gia 8 30 a m , 100 cc of water Venous blood	9–11	0 97	0 92	362	39 4	8 4	8 82	16
Exp A 29 Gia 6 a m , 30 grams urea and 500 cc of water 7, 8, 9, 10, and 11 a m , 500 cc of water each time Venous blood	9–10	2 17	2 06	362	71 9	10 3*		14*
	10–11	3 37	3 20	268	70 4	12 2*		16*
	11–12	4 17	3 96	209	69 0	12 1*		16*
Exp A-30 Gia 8 25 a m , 100 cc. of water Venous blood	9–11	1 17	1 11	435	49 9	9 7	9 19	17

TABLE 4

Summary of data concerning urea excretion

Subject	Diagnosis	Body weight	Augmentation limit Urine volume per minute	Standard blood clearance, $\frac{U}{B}\sqrt{V}$ (from points below augmentation limit): Number of observations	Maximum	Minimum	Average	Probable deviation from average		Maximum blood clearance $\frac{UV}{B}$ cor from points above augmentation limit: Number of observations	Maximum	Minimum	Average	Probable deviation from average	
		kgm	*cc*		*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*per cent of average*		*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*per cent of average*
Chi	Glomerulonephritis stage I	38	1.72	6	74.0	46.2	62.0	±6.2	±10.1	3	82.4	80.7	81.3	±0.6	±0.8
Jac	Glomerulonephritis stage I	56	2.11	15	25.6	18.6	22.1	±1.2	±5.6	9	35.6	28.6	32.1	±4.4	±13.8
Cic	Nephrosis	48	1.65	11	24.3	10.8	18.2	±2.5	±13.5	7	30.7	19.2	23.4	±3.1	±13.2
Val	Glomerulonephritis stage III	59	1.07	16	17.7	11.3	13.7	±0.9	±6.7	10	15.3	12.2	14.2	±0.8	±5.6
Gri	Glomerulonephritis stage III	64	1.97	10	9.19	6.47	7.98	±0.6	±7.9	4	12.2	10.2	11.2	±0.7	±6.6
Wol	Glomerulonephritis stage III	38	?	21	10.10	6.22	7.51	±0.7	±9.2						
Average			1.74						±8.8						±8.0
Probable deviation from average	cc per minute		±0.36												
	per cent of average		±20.5												

TABLE 4

Summary of data concerning urea excretion

Subject	Diagnosis	Body weight	Augmentation limit Urine volume per minute	Standard blood clearance, $\frac{U}{B}\sqrt{V}$ (from points below augmentation limit): Number of observations	Maximum	Minimum	Average	Probable deviation from average		Maximum blood clearance $\frac{UV}{B}$ cor from points above augmentation limit: Number of observations	Maximum	Minimum	Average	Probable deviation from average	
		kgm	*cc*		*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*per cent of average*		*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*cc blood per minute*	*per cent of average*
Chi	Glomerulonephritis stage I	38	1 72	6	74 0	46 2	62 0	±6 2	±10 1	3	82 4	80 7	81 3	±0 6	±0 8
Jac	Glomerulonephritis stage I	56	2 11	15	25 6	18 6	22 1	±1 2	±5 6	9	35 6	28 6	32 1	±4 4	±13 8
Cic	Nephrosis	48	1 65	11	24 3	10 8	18 2	±2 5	±13 5	7	30 7	19 2	23 4	±3 1	±13 2
Val	Glomerulonephritis stage III	59	1 07	16	17 7	11 3	13 7	±0 9	±6 7	10	15 3	12 2	14 2	±0 8	±5 6
Gia	Glomerulonephritis stage III	64	1 97	10	9 19	6 47	7 98	±0 6	±7 9	4	12 2	10 2	11 2	±0 7	±6 6
Wol	Glomerulonephritis stage III	38	?	21	10 10	6 22	7 51	±0 7	±9 2						
Average			1 74						±8 8						±8 0
Probable deviation from average	cc per minute		±0 36												
	per cent of average		±20 5												

In figure 7 the same urea excretion curve as the one given in figure 5 has been plotted on logarithmic paper In the logarithmic curve variations in height are proportional to *percentage* changes, rather than absolute changes, in the data plotted In a uremic case, the clearance values are all so low that variations on them are inconspicuous, when plotted on an ordinary scale, as in figure 5 But when plotted logarithmically, as in figure 7, they are as evident as the clearance variations of a normal subject

The values for the augmentation limits, given in table 4, are on the whole somewhat lower than those found for normal subjects in the preceding paper (6) The average figures for nephritic and normal subjects are 1 73 and 2 13 cc per minute respectively The decrease in augmentation limit is hardly great enough to justify the conclusion that it represents an effect of the disease It is not very significant compared with the relatively great fall in the *level* of the curves observed in cases with damaged renal function

In each case there is, compared with the normal, a fall of nearly equal proportions in the level of the ascending line and in that of the horizontal line reached at the augmentation limits, with relatively small change in the limit Consequently the standard blood urea clearance, indicated by the height of the ascending line at $V = 1$ cc per minute, and the maximum clearance, indicated by the height at the augmentation limit and beyond, show in these cases approximately equal percentage diminutions below the normal The similarity in the significance of results by the maximum and standard clearance determinations is also indicated by the agreement between the percentages of normal values shown by the two clearances for each individual, indicated by the figures with and without stars respectively in the last column of table 3

In table 4 the variations for the standard and maximum clearances in each patient are given The table shows that, as previously found with normal individuals, the average variation in a given subject is slightly greater for the standard clearance than for the maximum clearance

In figure 8 all the curves are presented, with scales indicating the per cent of normal standard and maximum clearance observed in each case It is apparent that both clearances tend to show about the same percentage fall in cases with renal deficiency

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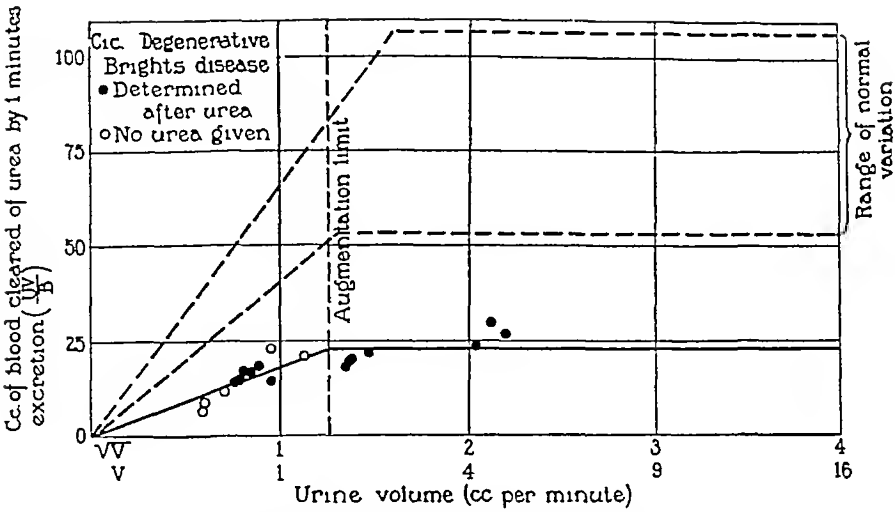


FIG 3 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT CIC.

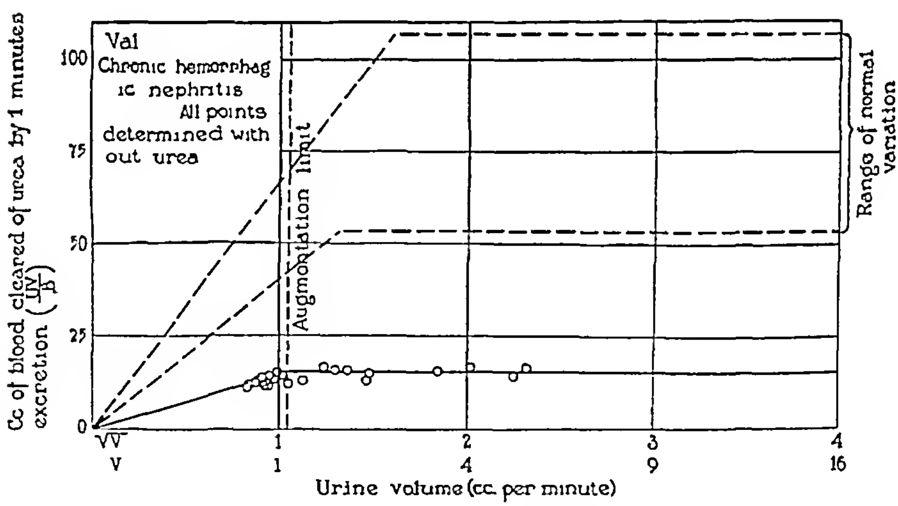


FIG 4 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT VAL

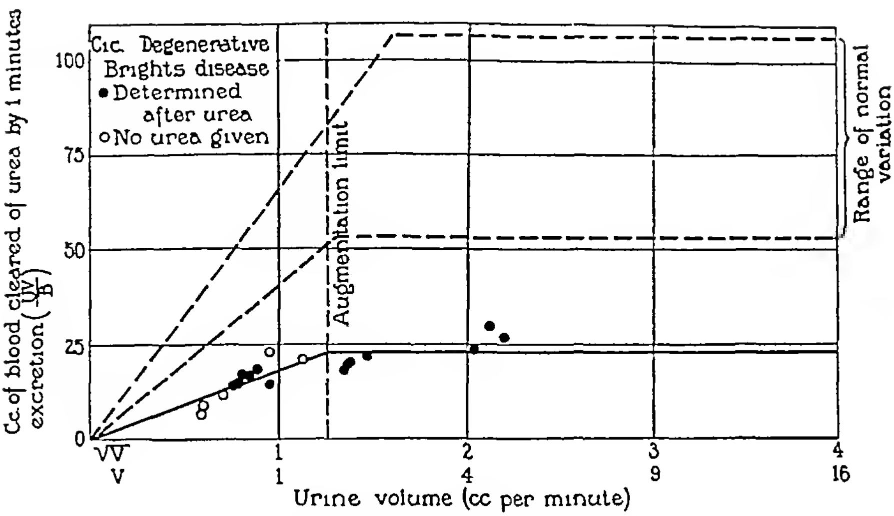
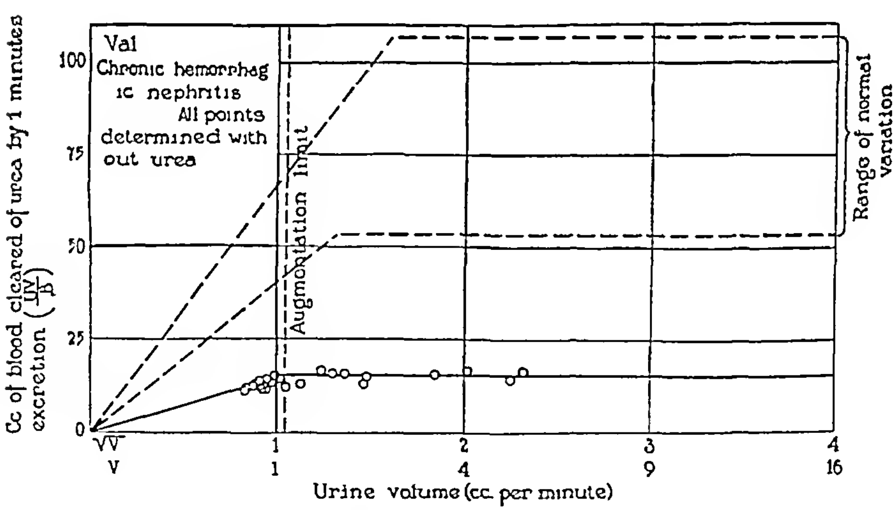


FIG 3 BLOOD UREA CLEARANCE CURVE, CORRECTED FOR BODY SIZE, OF PATIENT CIC.



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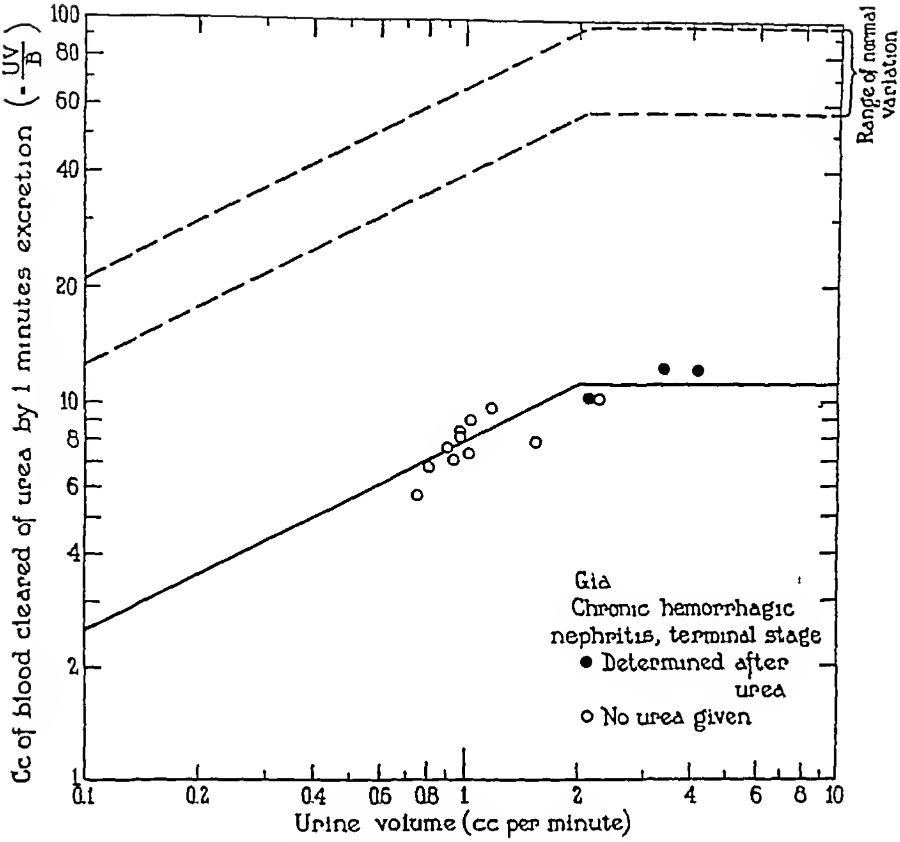

FIG 7 THE SAME UREA CLEARANCE CURVE AS THE ONE GIVEN IN FIGURE 5 BUT HERE PLOTTED ON LOGARITHMIC PAPER

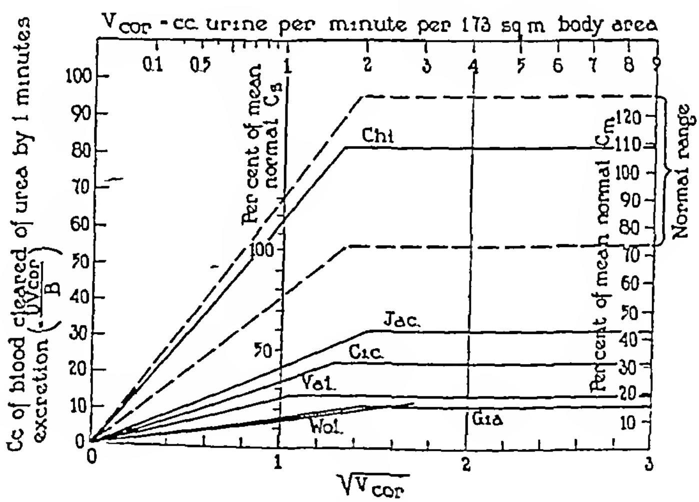

FIG 8 CURVES OF THE SIX PATIENTS, SHOWING RELATIVE EFFECTS OF RENAL DEFICIENCY OF EACH ON STANDARD AND MAXIMUM CLEARANCES

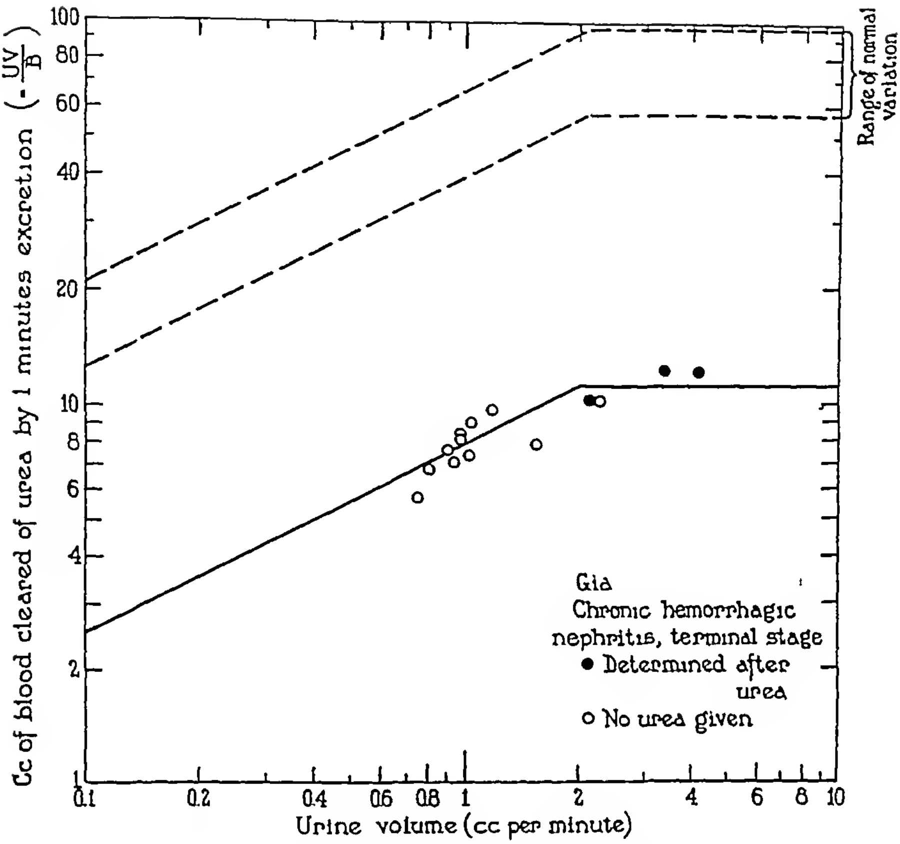

Fig 7 The Same Urea Clearance Curve as the One Given in Figure 5 but Here Plotted on Logarithmic Paper

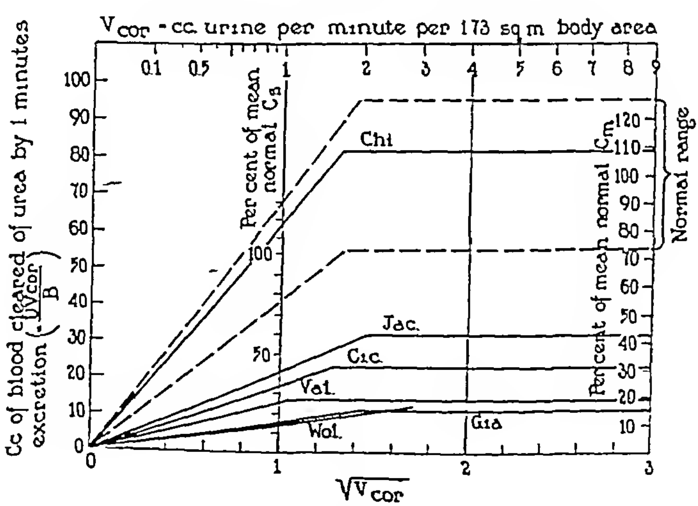

Fig 8 Curves of the Six Patients, Showing Relative Effects of Renal Deficiency of Each on Standard and Maximum Clearances

urine volumes above the augmentation limit of about 2 cc per minute, proved to be equally sensitive as indicators of renal function in these nephritics

4 Our data confirm MacKay and MacKay (3) in showing that loss of renal function may exceed 60 per cent before the blood urea content rises above the highest level observed in normal subjects Unless the excretion rate is also considered, the blood urea, taken alone, may fail to reveal diminishing renal ability until the latter has reached an advanced stage

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METHODS

In each experiment observations were made over a 24-hour period, from 6 a m one morning until 6 a m on the next day Hourly urine specimens were collected from 6 a.m until 10 p m , and then a single specimen was collected between 10 p m and 6 a m When the subject was unable to void or there was doubt concerning the completeness of voiding the hour period was extended to 2 hours A sample of blood was drawn by vein puncture at 6 30 a m , the middle of the first urine collection period, and then at the middle of each second hour thereafter until 8 30 p m The blood urea values for the intermediate hours were obtained by interpolation A sample was drawn at 9 30 p m for the last urine period of the day, and another at 6 a m on the following morning The average value of these two samples served as the blood urea concentration from which the standard clearance of the night period was calculated Urine collections were made within 2 minutes, and the blood samples were drawn within 5 minutes of the stated time The blood and urine urea concentrations were determined gasometrically (7) The standard clearance, $C_s = \frac{U}{B}\sqrt{V_c}$, where U is the urine urea concentration, B the blood urea concentration, and V the urine volume in cubic centimeters per minute, was calculated as previously described (4, 5) The urine volume, is corrected in each case to V_c by the use of a factor dependent on the ideal body surface of the subject On the charts the standard clearance has been recorded as the actual value and as a per cent of the normal mean of 54 cc per minute When V_c was above the augmentation limit of 2 the rate of urea excretion has been calculated on the basis of the maximum blood urea clearance, $\frac{U\sqrt{V_c}}{B}$ (5) These are recorded in the figures as a per cent of the mean normal, 75 cc per minute, but have not been used in determining the variability of the rate of urea excretion

The normal subjects on whom observations were made were up and about during the course of the experiments All of the patients suffering from Bright's disease were confined to bed None of the latter received any coffee with their meals, while the normal subjects

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Observations on 5 patients with degenerative Bright's disease are given in figure 3 With the exception of case no 12, one on whom

TABLE 1

Clinical and laboratory observations

Case number	Hospital number	Diagnosis: Bright's disease: Type	Diagnosis: Bright's disease: Stage	Complications	Age	Sex	Heart size	Blood pressure	Eye grounds	Edema	N P N (mgm. per cent)
5	6458	Hemorrhagic	Initial—latent	Acute sinusitis	49	M	Normal	155/106	Normal	0	35 0
6	6164	Hemorrhagic	Healed		31	M	Normal	125/65	Normal	0	20 0
7	6475	Hemorrhagic	Active		25	F	Normal	168/114	Normal	++	27 0
8	6139	Hemorrhagic	Latent		19	M	Normal	152/ 94	Normal	0	43 0
9	6162	Hemorrhagic	Latent		20	F	Slightly increased	202/115	Normal	0	25 0
10	6238	Hemorrhagic	Initial—terminal		16	M	Increased	136/ 86	Normal	0	64 0
11	6166	Hemorrhagic	Terminal	Cardiac insufficiency	34	F	Increased	203/118	Retinitis with hemorrhages	+	250 0
12	6184	Degenerative cryptic	Active		18	M	Normal	106/ 77	Normal	+++	23 0
13	6473	Degenerative cryptic	Initial		12	M	Normal	115/ 70	Normal	+++	23 0
14	6172	Degenerative cryptic	Active	Pulmonary tuberculosis	29	M	Normal	110/ 68	Normal	–	33 0
15	5949	Degenerative cryptic	Terminal	Empyema	20	M	Normal	128/ 83	Normal	+++	53 0
16	5505	Degenerative cryptic	Terminal		11	M	Normal	116/ 60	Normal	++	47 0
17	6446	Arteriosclerotic			49	F	Normal	234/154	Normal	0	44 0
18	6102	Arteriosclerotic			51	F	Slightly increased	148/ 86	Normal	0	[illegible]
19	6466	Arteriosclerotic		Cardiac failure	49	F	Greatly increased	242/145	Retinitis	+	57 0
20	5210	Hemorrhagic	Terminal	Otitis media	30	M	Normal	148/190	Normal	0	61 0
21	5482	Hemorrhagic	Active		12	M	Normal	152/110	Normal	+	22 0

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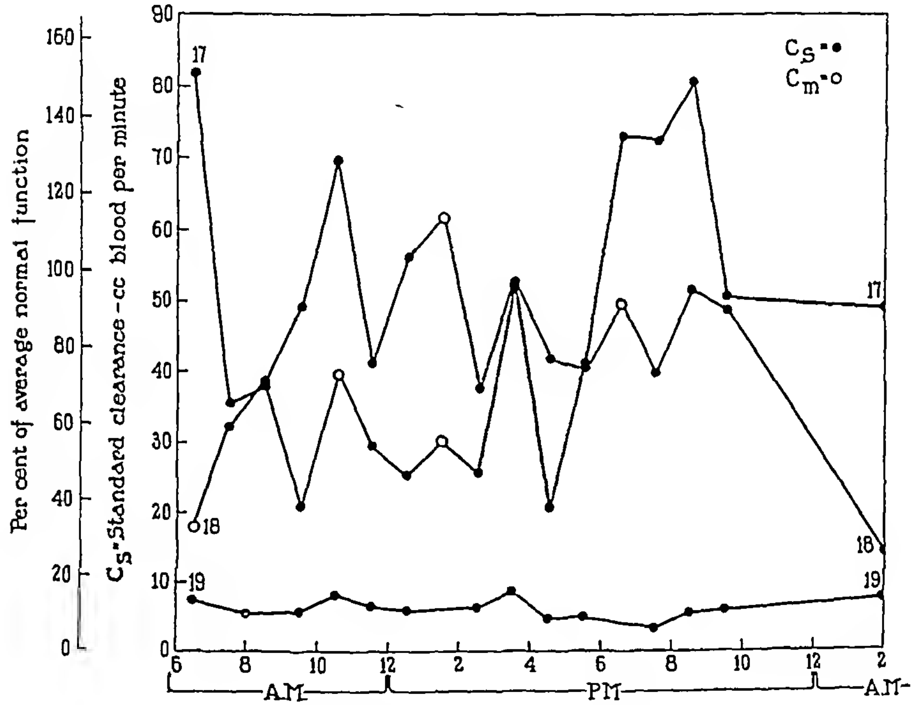

FIG 4 ARTERIOSCLEROTIC BRIGHT'S DISEASE

there appeared to be a decrease in the value of the clearance after both breakfast and lunch From the observations on patients no conclusion can be reached on this point

In order to ascertain whether it is necessary to carry out this urea excretion test in the fasting state a series of observations were made on two patients with hemorrhagic Bright's disease Observations were made for two hours, from 6 to 8 a m before breakfast, and for two other hour periods, 9 to 11 a m after breakfast The tests were

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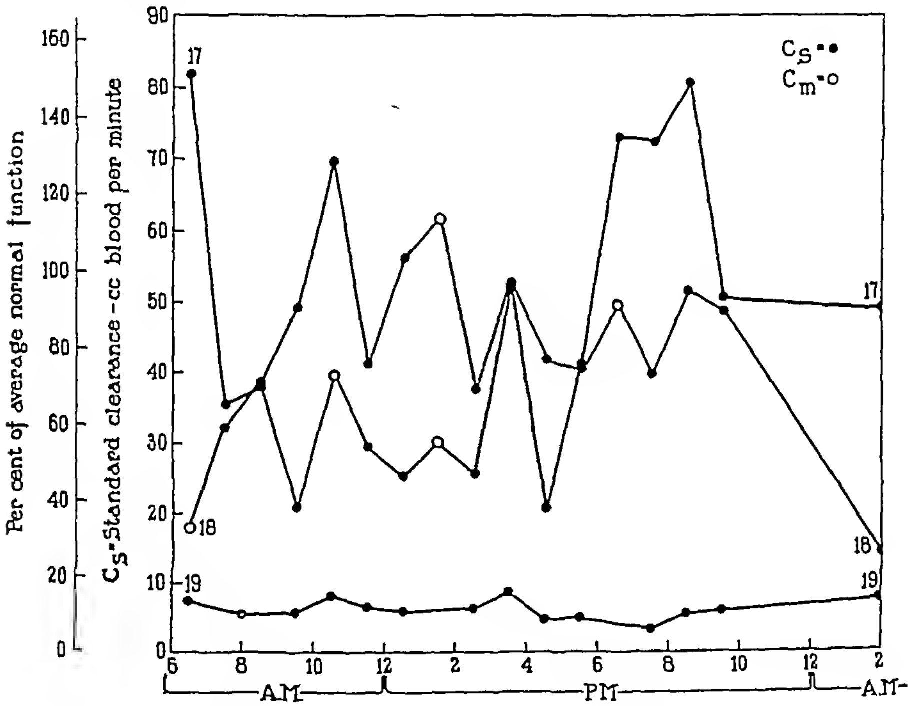

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made four days apart No coffee was given The results are given in table 3 Breakfast has no effect, for the volume of blood cleared of urea per minute was in each subject consistently the same before and after the meal The average figures show a slight increase in the post-breakfast figures, but it is not significant It is accordingly unnecessary to limit measurements of the standard clearance to fasting periods As additional proof that breakfast has no demonstrable effect, daily observations of the standard clearance were made between 8 and 10 a.m on a normal subject (no 2), and a patient (no 14) with degenerative Bright's disease On alternate days breakfast was omitted The results in table 4 show that there was no effect

The experiments detailed in table 3 indicate that there is less variability in a series of observations made on an individual on different days, but at the same time each day, then in a series of observations all made on the same day

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6 Moller, E, McIntosh, J F, and Van Slyke, D D, J Clin Invest, 1928, vi, 485 Studies of Urea Excretion IV Relationship Between Urine Volume and the Rate of Urea Excretion by Patients with Bright's Disease

7 Van Slyke, D D, J Biol Chem, 1927, lxxiii, 695 Determination of Urea by Gasometric Measurement of the Carbon Dioxide Formed by the Action of Urease

made four days apart No coffee was given The results are given in table 3 Breakfast has no effect, for the volume of blood cleared of urea per minute was in each subject consistently the same before and after the meal The average figures show a slight increase in the post-breakfast figures, but it is not significant It is accordingly unnecessary to limit measurements of the standard clearance to fasting periods As additional proof that breakfast has no demonstrable effect, daily observations of the standard clearance were made between 8 and 10 a.m on a normal subject (no 2), and a patient (no 14) with degenerative Bright's disease On alternate days breakfast was omitted The results in table 4 show that there was no effect

The experiments detailed in table 3 indicate that there is less variability in a series of observations made on an individual on different days, but at the same time each day, then in a series of observations all made on the same day

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The method, in brief, consists of the determination of total base, CO_2, Cl, inorganic phosphate and protein of serum The serum was obtained from arterial blood or venous blood (without stasis) which had been secured and treated, by techniques already described, in such a manner as to prevent all air contact.

The procedures for determining CO_2 and Cl have not been changed and the values for these factors previously given need no revision For total base a modification of Stadie's (3) adaptation of Fiske's method has been employed in the recent studies We have isolated and analyzed the benzidine sulfate instead of titrating the benzidine filtrate as Stadie recommended Previously reported base determinations were made by a technique in which phosphates were not removed, but were, supposedly converted to a form in which they combined

TABLE 1

Total base concentration in normal serum

Subject	Sex	Age	Total base
			m.-eq.
D M	Male	29	154 4
			157 2
			155 7
			156 3
H O	Male	27	153 0
F B	Male	30	153 6
L D	Male	27	152 5
M W	Male	30	155 0
E D	Male	26	153 0
J P	Male	40	154 0
A J	Female	28	153 0
R I	Female	31	152 5
H D	Female	15	158 0
A A	Female	16	152 0

with a definite equivalent of base Subsequent investigation showed that it was impossible to insure conversion of phosphates to such a stable form with any regularity

Earlier base determinations were subject to an error, the magnitude of which depended upon the amount of inorganic phosphate in the serum, varying from +1 to −1 equivalent of base for every equivalent of P in serum As the serum of normal resting adults contains only from 1 to 3 milliequivalents of inorganic P, the error is of little significance It may, however, attain a considerable magnitude in subjects with advanced chronic nephritis with high serum phosphates

Fifteen analyses of the sera of 11 normal young adults (medical students, physicians and laboratory workers) carried out by the new technique in this laboratory by Oard and Lee reveal a greater constancy in the concentration of total base than did the determinations reported earlier See table 1

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ratio is abnormal, calculations based on determinations of total protein only and assumption of an average ratio may be subject to significant errors Such errors are of little importance in dealing with normal blood as can be seen in table 2 They might attain a considerable importance in pathologic conditions associated with abnormal serum albumin globulin ratios Fortunately in these conditions the total protein concentration is usually low and the error correspondingly diminished

The present work has included determination of serum pH only in rare instances For the purposes of calculating base combined with protein an average pH value of 7 35 has been assumed The equations given above are, therefore, simplified to

$$BP_{(alb.)} = 2\ 733\ P$$
$$BP_{(glob.)} = 1\ 869\ P$$
$$BP_{(prot.)} = 2\ 476\ P\ (A/G = 1\ 8)$$

Such simplification, although obviously necessary if the total procedure is to be made generally applicable to the study of clinical problems, introduces into the calculations another error

Phosphate combining equivalents are also calculated with the assumption of a constant pH of 7 35 At this pH 80 per cent of the phosphate exists in the dibasic form pH and the ratio $\frac{HPO_4}{H_2PO_4}$ vary in the same direction, as the reaction of the blood changes

The total errors entailed in the assumption of a constant pH are seldom of important magnitude If inorganic P were as high as 19 mgm per 100 cc and pH as low as 7 00, phosphate equivalents calculated by the formula that has been employed would give a value only 1 m eq too high If in the same serum the total protein concentration were 7 00 per cent, the value obtained for BP would be 2 5 m eq too great If the A G ratio were only 1 0, a further positive error of 1 5 m eq would be introduced The total error in this extreme case in the estimation of base combined with protein and phosphate would be +5 0 m eq with a negative error of the same magnitude in the undetermined acid value In the actual analyses presented errors never attained such magnitude because high phosphorus and low pH were usually associated with reduced proteins

The new "total base" method was introduced in November, 1925 In the tables, then, base values of earlier dates may be in error by as much as the equivalents of inorganic P found in the serum If proteins were fractionated it is indicated in the tables When non-protein nitrogen of serum has been determined it is indicated in the tables by the letter *s* after the non-protein nitrogen value In all other instances whole blood non-protein nitrogen has been used for correction of the serum protein values

If the newer factors and methods are employed for the estimation of the acid-base equilibrium of serum the concentration of the base combined with "undetermined acids" (sulfate + organic acids) seldom exceeds and is usually considerably less than 10 milliequivalents

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TABLE 3

Data in nephritic patients

Number	Date	Weight	Edema	Vomiting	O_2 capacity	Cell volume	1 Serum total protein	2 HCO_3	3 Cl	4 Inorganic P	5 Acid 1+2+3+4	6 Base	Undetermined acid 6 − 5	Non protein nitrogen	Phthalein per cent in 2 hrs.	Treatment and remarks
	1924	*kgm*			*volumes per cent*	*per cent*	*m eq*	*m eq*	*m eq*	*m eq*	*m eq*	*m eq*	*m eq*	*mgm per 100 cc*		
29267	February 19	67.8	0	0	14.8	29.4	16.5	19.0	102.7	3.1	141.3			85	18	
	February 25	66.4	0	0	15.0	32.6	17.5	18.1	100.0	2.9	138.5			75		After salt poor diet
	February 29	66.0	0	0	14.3	32.5	16.7	18.8	105.3	3.2	144.0			69		After 2 days of low fluid + 5 grams NaCl
	March 8	68.2	0	0	13.8	31.3	15.5	19.5	104.4	2.2	131.6			44		After 8 days of high fluid + 5 grams NaCl
	1925															
	January 14		0	0	12.7		17.1	16.3	109.0	6.5	148.9	183.7	34.8	75		Ambulatory. Without symptoms
	November 19	59.0	0	+	8.7	23.0	16.4	9.8	105.5	5.5	137.2	173.0	35.8	167	<5	Uremia
	November 27	59.0	0	+	8.4	21.3	15.6	8.2	96.4	5.4	125.6	132.9	7.3	168		
	December 1		0	+	7.3	17.1	12.6	13.3	95.3	5.4	126.6	148.0	21.4	167		Coma. Bicarbonate and saline on November 30
	December 6		0	+	5.9	17.1	15.3	14.2	96.2	7.4	133.1	137.5	4.4	163		Convulsions. Before and after intravenous $MgSO_4$
					6.3	16.3	15.3	12.6	94.3	7.4	129.6	140.6	11.0			
	December 11		0	+	4.9	15.3	13.9							158		Before and after intravenous $MgSO_4$
					5.4	15.4	13.9									
	December 17		0	0	7.4	20.0	14.5	10.5	102.4	4.8	132.2	133.6	1.4	145		Rational. Free from symptoms. After frequent subcutaneous saline
	1926															
	January 2	51.8	0	+	7.1	18.3	16.1	6.8	94.4	5.7	123.0	128.1	5.1	165		Ascending urinary infection. After 10 days of negative Cl balance
	January 9			+	5.1	14.9	11.1	4.5	90.8	5.6	112.0	120.5	8.5	171		Heart failure. Comatose. Has received subcutaneous NaCl. Died January 11
	1927															
60345	April 20	52.7	+	+	7.2	20.5	14.6	17.3	102.4	3.5	137.8	148.2	10.4	117	<5	Heart failure
	April 25	49.1	0	+	8.0	17.7	15.5	16.5	103.2	5.0	140.2	148.0	7.8	122		After diuresis and negative Cl balance
	May 3	49.8	0	+	6.7	17.6	15.8	16.3	105.6	4.2	141.9	145.9	4.0	118		Positive Cl balance
	May 10	51.6	0	0	6.8	17.3	13.4	16.8	106.6	4.2	141.0	149.1	8.1	112		Positive Cl balance
	May 17	51.4	0	0	5.0	16.1	14.9	16.3	110.0	4.9	146.1	154.5	8.4	124		Cl equilibrium
	May 27	51.2	0	+	5.7	17.5	15.4	17.8	103.8	4.7	141.7	150.5	8.8	123		Negative Cl balance
	June 7	51.2	0	0	6.6	19.8	15.7	17.1	107.6	4.7	145.1	153.4	8.3	94		Positive Cl balance
	June 17	53.5	0	0	6.8	19.9	12.7	15.8	107.0	4.7	140.2	148.8	8.6	98		Positive Cl balance. Died some months later
	1926															
56247	December 27	65.7	+	+	10.7	41.8	12.5	25.0	106.8	3.5	147.8	154.3	6.5	85		Heart failure

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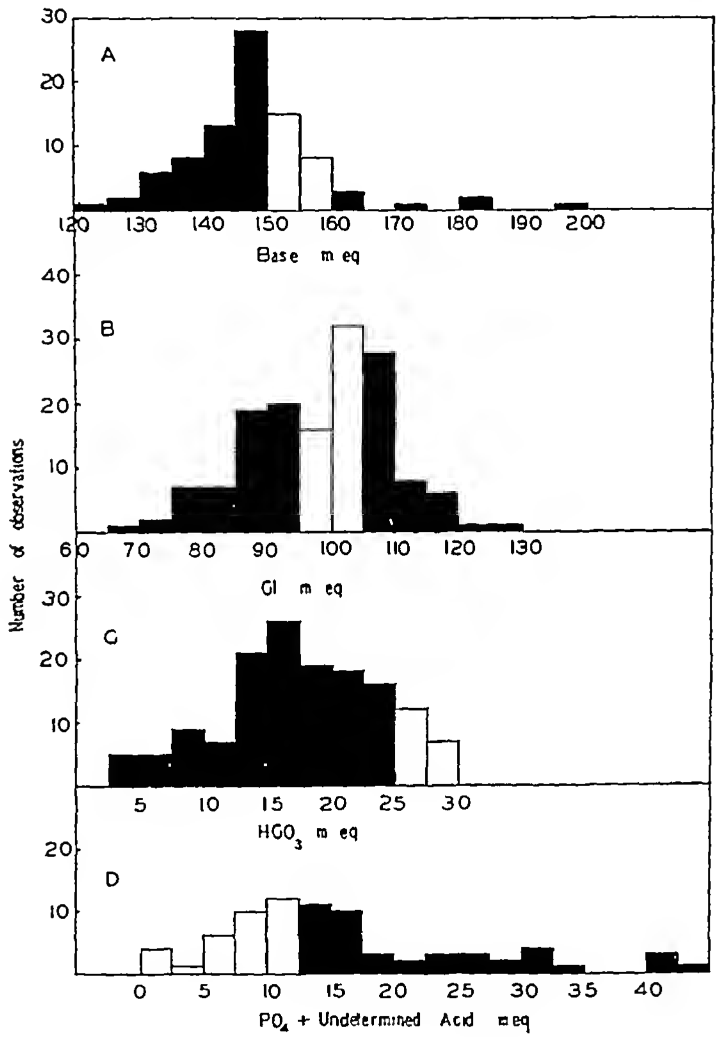

FIG 1 DISTRIBUTION OF VALUES FOR BASE, Cl, HCO_3 AND PO_4 + UNDETERMINED ACID

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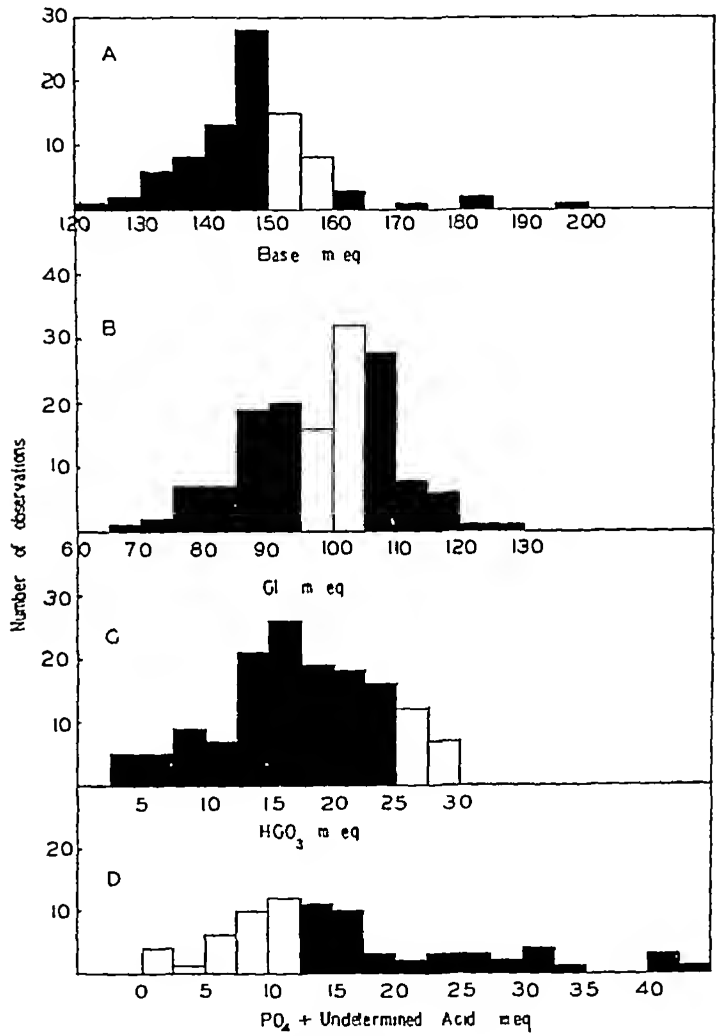

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Phosphate, sulfate and organic acid as causes of acidosis

Figure 1 D shows the frequency with which excessive quantities of PO_4 + undetermined acids are encountered That PO_4 accumulation alone offers an inadequate explanation of nephritic acidosis has already been mentioned Denis and associates (8) and others (9) have shown that the inorganic sulfate content of blood is often greatly increased in chronic nephritis with nitrogen retention More recently Atchley (10) found that, after complete ablation of kidney function, both PO_4 and SO_4 accumulated in the serum and that the increases of these two ions accounted for the reduction of the concentrations of HCO_3 and Cl In the present work no attempt has been made to estimate SO_4 directly It is, however, included in the "undetermined acid" fraction Figure 1 D, while proving that excessive PO_4 + undetermined acid values occur, also shows that the increases are far less frequent and usually of smaller magnitude than CO_2 reductions This would prove, as far as statistical treatment can prove, that accumulation of inorganic phosphate, sulfur, organic acids or any combination of the three affords an entirely unsatisfactory explanation of nephritic acidosis as a whole, although any one of them exist and act as a contributory factor in individual instances Figure 2 more specifically demonstrates the absence of any definite relation between PO_4, undetermined acid and HCO_3 in observations in which all were determined

Analysis of data from individual cases shows that high undetermined acid occurred, with few exceptions, only when vomiting was an important symptom and on this account or another patients had not received adequate carbohydrate and fluids by mouth or by parenteral routes It was more frequently encountered in the cases observed early in the study when the administration of carbohydrate fluids was not so vigorously pushed, it often failed to appear even in the premortal state when large amounts of carbohydrate and fluid were given, and it often disappeared rapidly after their administration

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Even if accumulation of phosphate and sulfate in the blood were responsible for or regularly associated with the observed bicarbonate reductions, it would still be impossible to ascribe the phosphate and sulfate accumulations directly to failure of the renal excretory function Such an explanation involves certain assumptions that phosphates and sulfates are obligatory excretory products for the elimination of which the organism is dependent upon the kidney, and that, in advanced renal disease, the urinary excretion of these substances is diminished As far as phosphate is concerned, neither of these assumptions is supported by experimental work Phosphate is largely excreted in the feces as well as the urine and its partition between feces and urine seems to be determined chiefly according to the needs of the organism for the elimination of acids or bases Its level in the blood can be altered without appreciable effect on its excretion in the urine (12) and its elimination by the kidneys can be completely or almost checked by procedures that have no demonstrable injurious effects upon the kidneys (13) Even if it were granted that the phosphate accumulations in the serum of dogs after complete ablation of kidney function demonstrated by Atchley (10) were a direct result of the animals' inability to excrete phosphorus in the urine, it remains doubtful whether such extreme experiments have any important bearing on the problem of clinical nephritis The deduction that similar accumulations observed in dogs after pyloric obstruction are due to renal injury (14) seems unwarranted

Boyd (15) found that nephritic children with high serum phosphate showed negative phosphate balances on diets containing small, but adequate amounts of phosphorus One experiment performed by Fetter (16) has an interesting bearing on the whole problem of the relation of hyperphosphatemia to acidosis and renal function in nephritis Fetter administered disodium phosphate to a nephritic patient with high serum phosphate and low bicarbonate As a result serum bicarbonate was restored to the normal level and urinary phosphate increased, but serum phosphate remained unchanged

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analytical errors because excellent duplicate checks were obtained and because similar values have been found in no examinations in the normal series or in non-renal pathological subjects Furthermore, it is more than a peculiar coincidence that two of the high bases should have been found in one individual, 29267, at an interval of 10 months In only one instance (29267, November 19, 1925) was high base found at a time when a patient presented serious symptoms or evidences of uremia In this one exceptional instance base was presumably falling, with the rather acute development of uremic manifestations and vomiting, from a still higher level

As to the causes for high base concentration the data available are altogether too meager to permit any entirely satisfactory conclusions High base occurred only when patients were or had recently been outside of the hospital on comparatively unregulated diets In one case, 33247, administration of large amounts of fluid, with the production of water diuresis without salt restriction, was followed by reduction of the base concentration to the normal level within a week One gains the impression that the insufficient kidney is unable to excrete large quantities of base unless large amounts of water are simultaneously made available

Low base is encountered far more frequently than high base and is especially prone to develop in the uremic state As base may be considered a measure of the total electrolyte concentration of the serum, it is also a measure of the substances normally responsible for the determination and maintenance of the osmotic pressure of the serum On this account it has been suggested that the total electrolyte (base) deficiency in the serum in nephritis is an adaptive reaction to compensate for the presence of an abnormal excess of organic molecules, such as the end products of nitrogenous metabolism, which accumulate in the blood as the result of renal insufficiency Gram (17) and others have, in point of fact, demonstrated, in certain cases of nephritis with nitrogen retention, diminished serum conductivity with normal or excessive freezing point depressions A similar association of high non-protein nitrogen and low base is found in pyloric obstruction Because, from the nature of the condition, it seems logical to presume that the reduction of base is the primary change, Hartmann, Scott and Moser (18) have sug-

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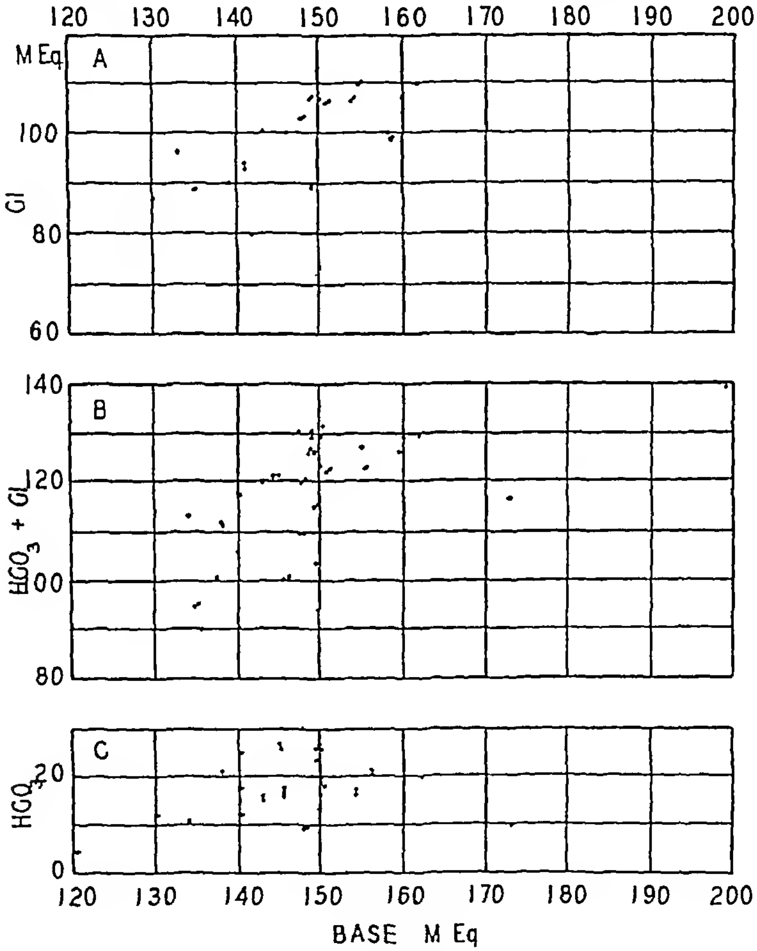

FIG 4 Cl, HCO_3 + Cl AND HCO_3 PLOTTED AGAINST BASE

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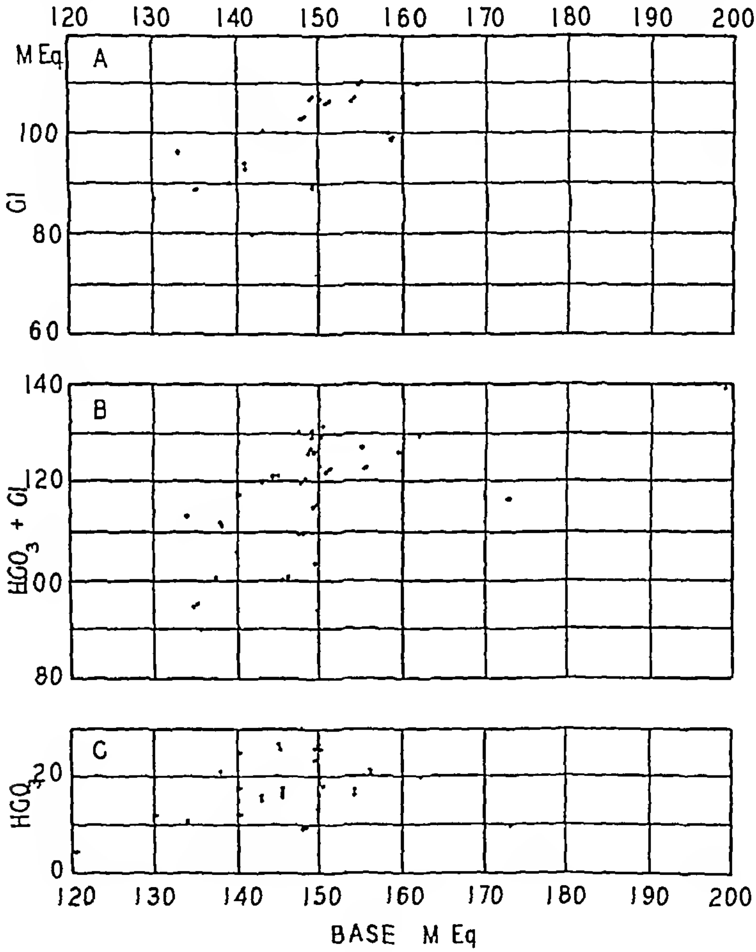

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spite of the fact that both Cl and PO_4 + undetermined acid are often elevated This explains the fact that HCO_3 never exceeds the normal limits

If the determinations with high base only are considered it appears that the acids that combine with the excess are Cl or undetermined acids Among the cases with low or normal base one finds a few in which Cl is above the normal level with HCO_3 proportionately reduced Both these groups conform to the type which Blum, Delaville and Van Caulaert (21) and others have spoken of as "dry chloride retention" Such a term, however, carries the unproved implication that the hyperchloremia is a primary change, the result of inability of the kidney to excrete the chloride ion

In most cases in which Cl is low, base is also diminished, the converse is not, however, as consistently true HCO_3, alone may bear the brunt of base reduction

It is evident that most of the disturbances described can be included under the general term "acidosis," if the latter is used in the sense in which Van Slyke has employed it to describe those conditions in which there is a deficiency of bicarbonate (or base not bound by acids other than carbonic) It is clear, however, that such a simple term hardly does justice to the great variety of electrolyte patterns observed in nephritis Such reductions of bicarbonate may be associated with total electrolyte deficiency (low total base), high Cl, high phosphate, high undetermined acid, or a combination of two or more of these factors It is also clear that profound disturbances of electrolyte equilibrium may occur without any serious alteration of bicarbonate, especially if base is high It would seem obvious that more than one factor must be responsible for the production of so many diverse patterns and that, to be rational, therapy must take these factors into account

Pathogenesis of electrolyte changes and their therapeutic implications

In discussing the subject of pathogenesis of electrolyte change and their therapeutic implications use will be made of certain metabolism data which are presented in the succeeding paper In the last column of Table 3 when it is noted that the Cl-balance was negative it means that the Cl in the excreta collected exceeded that in the food and

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It has been suggested that the hypochloremia of nephritis is due to transfer of Cl from blood and body fluids to the tissues, where it accumulates in excess In dogs deprived of kidney function Atchley (10) was unable to detect such accumulations in any tissues which he analyzed In our own studies, when all excreta were collected and analyzed it proved possible to account for changes in the level of serum Cl from observed salt and water balances There would seem to be, in the most severe stages of nephritis with uremia, a loss of the ability of the organism to maintain the usual equilibrium between salt and water excretion and to maintain the concentration of these substances in the serum at the normal constant level Cl continues to appear in the urine in relatively large amounts even when serum Cl has fallen far below the normal level and even below the level which has been called by Ambard the threshold of chloride excretion

On the other hand, by giving large amounts of salt, it is possible to maintain Cl at the normal level or to restore it if it is reduced It is even possible to push it above normal, especially if the fluid intake is not increased in proportion to the salt Apparently the ability to eliminate large amounts of salt, especially in the absence of a proportional amount of water available for urine formation, is impaired

In general serum base concentration follows that of Cl, although there are distinct exceptions to this rule From this one can infer that chloride is largely excreted as BCl Unfortunately, because of technical difficulties, base balances have been determined in no cases Base is often reduced when Cl is normal or high and is sometimes high in relation to Cl These exceptions to the general rule of parallelism between these two factors are probably referable to the accumulation of other acids that may specifically depress Cl, on the one hand, and impairment of the mechanism for the formation of ammonia on the other Because of the latter the organism is forced to employ fixed base to neutralize any acid products of metabolism excreted in the urine

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with uremia, enough salt must also be given to prevent salt depletion How much salt should be given is another question The authors have found that in cases in which there is no tendency to waste salt by extrarenal channels, 7 to 10 grams of NaCl daily (that is, 5–7 grams added to a salt-poor diet) is sufficient, if the urine volume is 2000 to 3000 cc If because of previous misdirected dietary therapy or restriction of fluids, dehydration or salt depletion or both already exist, larger amounts of salt are required at first to overcome deficiencies and to permit the retention and storage of water without dilution of the electrolytes of serum and tissues

Undoubtedly such treatment will, at times, result in the production of or aggravate an already existing edema In this series edema was never observed, even after the subcutaneous administration of large amounts of saline, unless there were present obvious signs or symptoms of heart failure This is generally recognized to be the rule in these patients, who ordinarily have a definite tendency to diuresis The aim of forcing fluids and salt is to overcome and prevent dehydration and to promote the elimination of a large urine volume Obviously, in the presence of heart failure, oliguria and edema, this end can not be effected unless cardiac compensation can be established However, fluid restriction even in these cases should be moderate and can only be considered as a temporary expedient Metabolism does not cease and the production of metabolites, the retention of which is the presumable cause of uremia and death in these cases, continues whether urine is excreted or not, with the result that these substances accumulate in excess in the body during periods of oliguria The only salvation for such patients is the elimination of an adequate urine volume Unless this can be induced by rest and digitalis a fatal outcome is inevitable

The large amounts of fluid lost by extrarenal channels are often forgotten in the treatment of these cases Loss of water by lungs, sweat, vomitus and bowel is of little benefit to the organism in the elimination of metabolic products That this is becoming more and more generally accepted theory is evidenced by the ever diminishing use of so-called "depleting measures" In nephritis with edema from heart failure dyspnea is a striking feature, often the result of fixed acidosis as well as of the factors active in the production of cardiac

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In certain instances, then, base reductions develop in excess of Cl deficit, perhaps because base is wasted in the urine for the neutralization of foreign acids, since ammonia is unavailable Under these circumstances bicarbonate administration is indicated It is not, however, rational to attempt to restore base deficiency in general, or low CO_2 capacity due to other causes, by bicarbonate therapy Ellis (22) has pointed out the tendency of nephritic patients to develop alkalosis and tetany, if they are given bicarbonate when it is not clearly indicated

A word should, perhaps, be said about the serum proteins in relation to acid-base equilibrium, although the general subject of the proteins in renal disease will be treated in a separate publication The concentration of serum proteins is extremely variable, but more often low than high and, therefore, can not be held responsible for reductions of HCO_3 or Cl The rapid variability of the proteins suggests changes in the water content of the blood

SUMMARY

Studies of the total electrolyte equilibrium of the serum have been made on a large series of patients with serious renal damage due to nephritis, vascular disease and "surgical" kidney conditions

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On admission he appeared pale, wasted, dehydrated, somewhat stuporous, breathing rapidly and heavily, with face and extremities twitching His heart was enlarged, his systolic blood pressure 180, diastolic 115 He had advanced albuminuric retinitis

Administration of adequate calories and fluids by mouth failed because of continuous vomiting His stupor deepened to coma and he finally developed convulsions

At the time of the 14th study, December 17th, he was much improved, rational, and taking food and fluids by mouth without vomiting December 22nd, he was able to sit up in a chair

December 24th he was seized with pain in the flanks, urgency and dysuria, and pus was found in his urine After this he became rapidly worse

At the time of the last examination, January 9th, he was again stuporous and vomiting His breathing was labored and stertorous and profuse râles were heard over both lungs He died January 11th

The urine showed a specific gravity constantly low, 1 002 — 1 010, a variable amount of albumin, casts and red cells After December 24th, 1925 it became frankly purulent

He had a progressive anemia, his red blood cells and hemoglobin falling from 4 7 million and 80 per cent, respectively, to 1 5 million and 45 per cent in the course of his disease

Autopsy revealed Scars of kidney with glomerular adhesions and atrophy and hypertrophy of tubules Subsidiary Cardiac hypertrophy Fibrosis of myocardium Focal pneumonia Arteriosclerosis Acute cystitis

Case no 60345 A married American woman, aged 21, was admitted to the hospital April 16, 1927

During the preceding year she had developed increasingly frequent headaches, dyspnea on exertion, cardiac palpitation, polyuria and nocturia Very recently puffiness of the face, swelling of her legs, pain and swelling of her throat had appeared, attended by a racking non-productive cough, diffuse backache and dull headache, and later vomiting As the vomiting increased the edema diminished, but other symptoms, including dyspnea, became aggravated

She appeared acutely ill, anxious and distressed, pale, cyanotic, with marked dyspnea and orthopnea, tachycardia and a blood pressure of 180/120 There was some puffiness about the eyes, extremities and trunk, but no definite edema The heart was much enlarged, with a rough systolic murmur at the apex and accentuation of the aortic second sound Over the bases of both lungs there were dullness and numerous râles, especially on the left side where the breath sounds were somewhat suppressed The liver was large and tender There were no significant retinal changes

With rest, digitalis, and dietetic treatment she improved greatly and was discharged on June 26th She was readmitted August 31st, in a stuporous condition

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At the time of the second study the arthritis was subsiding By May 6th, when he was free from arthritis, the blood non-protein nitrogen had fallen to 58 mgm per 100 cc He was discharged in this condition, greatly improved

The third examination was made May 28th, when he returned to the dispensary in another acute attack of arthritis He did not return again

His urine showed a specific gravity of 1 005 to 1 012 At first there was much albumin and many red blood cells, but these diminished as the acute attack of gout subsided

Blood counts 4 1 to 3 6 million red blood cells, 85 to 60 per cent hemoglobin, 17,200 to 4,900 leucocytes

Case no 36041 A single male, aged 29, was admitted to the hospital February 23, 1925

He was reported to have had acute nephritis in 1909, and after 1918 albumin and casts were repeatedly found in his urine February 23, 1925, his blood pressure was 172/115, but it fell to 142/110 by March 4th when he was discharged Physical examination was otherwise negative except for a small tophus on the right ear, and the patient was free from all symptoms

In August 1925, he had an acute attack of gout lasting four or five days and relieved by cinchophen

From April 1925 on he complained of more and more persistent suboccipital headaches, which continued in spite of medication His systolic blood pressure also remained more consistently high and the diastolic pressure rose

October 15th, 1926 the blood was examined again because of the persistent headache and he was ordered a diet restricted in both protein and salt The fourth blood study was made November 12th, after he had been on this diet for almost a month The fifth examination was made a month later when he had relaxed his diet The third, fourth and fifth were all made while the patient was out of the hospital and the diets were never strictly controlled The changes in dietary salt did not influence his symptoms

His condition continued with little change until May 1927, when he began to complain of occasional cardiac palpitation During the succeeding summer he went away for a month's vacation and, during this, was somewhat relieved of his headaches and other symptoms However, they recurred as soon as he resumed his normal life

After the latter part of December 1927, he had increasingly frequent attacks of cardiac palpitation and dyspnea In March 1928, he also developed anorexia and nausea, with occasional vomiting

April 7th he began to vomit at frequent intervals and the following day developed arthritis of the left great toe His breathlessness and headache had, meanwhile, improved The arthritic pain was rapidly relieved by cinchophen, but vomiting continued About two weeks later he developed a cough and his dyspnea returned

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His condition continued with little change until May 1927, when he began to complain of occasional cardiac palpitation During the succeeding summer he went away for a month's vacation and, during this, was somewhat relieved of his headaches and other symptoms However, they recurred as soon as he resumed his normal life

After the latter part of December 1927, he had increasingly frequent attacks of cardiac palpitation and dyspnea In March 1928, he also developed anorexia and nausea, with occasional vomiting

April 7th he began to vomit at frequent intervals and the following day developed arthritis of the left great toe His breathlessness and headache had, meanwhile, improved The arthritic pain was rapidly relieved by cinchophen, but vomiting continued About two weeks later he developed a cough and his dyspnea returned

sharp kyphosis of the lower dorsal and upper lumbar spine, knee jerks and ankle jerks were absent and both legs were definitely atrophied, though not paralyzed A periurethral abscess was found, discharging pus, blood and urine The next day this was opened wide and was found to extend into the ischiorectal fossa and to the epididymis March 5th some abscessed teeth and roots were removed under gas and oxygen

After this he was unable to take fluids, became more and more stuporous and, by March 8th, when the first blood examination was done, was in coma, with deep, labored respirations

Intravenous glucose was given with some benefit on this day and on the next intravenous glucose and subcutaneous salt and glucose The second study was made on March 10th, after this treatment The treatment was repeated on the 10th, and on the 11th and 12th intravenous sodium bicarbonate was given as well By March 11th he was much improved, conscious and able to take fluids by mouth The third study was made on the 13th, after this treatment After this, intravenous and subcutaneous treatments were stopped because he was able to take food by mouth His salt and fluid intake fell somewhat lower, but he seemed relatively well when the last study was made, on March 19th and when he was discharged on March 21st However, he died about three weeks later at home

Autopsy was not obtained

Case no 20921 A married woman, aged 35, was admitted to the hospital February 26th, 1925

In 1914, 1919 and 1922, the last time following a pregnancy, she had had cystis and bilateral pyelitis

February 22nd, 1925 she developed dizziness and blurring of vision, vomited, and felt feverish and weak Three days later she "fainted" several times February 28th severe headaches, dyspnea and palpitation began with extreme frequency of urination, thirst and vomiting The next morning she had two convulsions for which she was sent to the hospital On admission she appeared sick, anxious and restless and complained of severe occipital headache Both optic discs were swollen and there were hemorrhages in both retinae The heart was not enlaged, the blood pressure was 200/150

Her urine showed a specific gravity of 1 010, heavy albumin, numerous casts and leucocytes

The first blood examination was done when she entered the hospital She was given large amounts of carbohydrate containing fluids and salt for the first day and then a diet somewhat restricted in protein, but high in fluids and salt She improved rapidly and by the time of the second study, March 9th, was eating her diet well and feeling quite fit She was discharged on March 15th After this she was followed in the Dispensary

She was again in the hospital for vomiting and convulsions, October 12th to

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7 de Wesselow, O L V, Lancet, 1924, i, 1099 The Inorganic Constitutents of the Blood in Certain Pathological Conditions

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In earlier studies salt poor diets or salt poor diets to which a known amount of salt had been added were given The Cl in such salt poor diets, estimated by the aid of the usual tables of food composition never exceeded 35 mM (2 grams of NaCl) daily Although low or falling serum Cl was usually attended by negative Cl-balances when patients were on salt poor diets, the addition of Cl to such diets sometimes resulted in positive Cl balances although serum Cl continued to fall More rigid dietary control was therefore instituted

All diets were prepared salt poor in the diet kitchen and their Cl-content carefully calculated from the best available food tables Extra salt, carefully weighed, was provided in small flasks from the laboratory, to be added to the food during the day by the patient Food refused by the patient was carefully reweighed, the salt and nitrogen in the refusals estimated and subtracted from the salt offered The flasks were also reweighed in the laboratory at the end of the day if the extra salt had not all been used

The decision to put added salt on the food in the wards was taken because it was appreciated that if such additions were made in the diet kitchen it was practically impossible to insure the complete transfer of the salt from cooking utensils to dishes, because such a technique required the separate preparation of each article of diet for every individual, and because it required separate weighing of the salt to be used on each individual dish in the diet On the other hand, with the system adopted, if a patient was unable to eat any of the food he had salted it was impossible to estimate the amount of salt refused As both appetites and digestions of some of these patients were most capricious, such occurrences were not uncommon If salt thus lost were neglected apparent positive balances would result When salt was given subcutaneously or intravenously, as it was in some of the most severe cases, salt intake could be calculated with considerable accuracy

At first urine alone, collected with all the usual precautions, was analyzed for nitrogen and Cl Attempts were also made to collect all vomitus, with only partial success In later experiments great efforts were made to collect all excreta, urine, vomitus and feces

Special urinals and bed-pans were provided by the laboratories to the wards All specimens of urine, vomitus or feces were brought to the laboratory and placed immediately in the refrigerator in the receptacles in which they were originally collected In the laboratory these specimens were quantitatively transferred, measured and subjected to analysis If the stools were contaminated by urine, a surprisingly common occurrence considering the precautions taken against it, the urine was decanted and treated with the other urine

Urine, feces, and vomitus were analyzed for both nitrogen and chloride Urinary nitrogen was determined by the usual Kjeldahl procedure, Cl by Volhard-Harvey titration In some of the earlier studies of vomitus Cl was determined in the same manner, while total and free acid were titrated with phenolphthalein and

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TABLE 1

Patients with hypochloremia

Number	Date	Serum Cl	Serum Base	Vomit	
		mM	*mM*		
26672		74 6		++	Urinary retention
14188	December 9	127 1		+	
	December 16	78 6		+	Water without salt
18826		80 7		+	
26555	December 10	95 1		+	
	December 12	90 1		++	
29522	March 6	91 8		++	Urine contained little salt, but patient received practically none
	March 17	89 6		++	
	April 1	92 6		++	
29039	January 25	109 5		+	On admission
	January 26	88 6			After fluids, including subcutaneous saline
	January 27	97 4			After bicarbonate, saline and glucose
	January 28	98 5			After further glucose and saline
33049	April 26	86 8		+	
	April 30	86 8			Fluids without salt
26409	November 20	82 9		++	
	November 28	82 9			After salt poor diet. Negative Cl balance from urine alone
	December 5	87 5		+	After 7 days with low fluids and 7 grams of extra salt
	December 17	81 9		+	After 2 days of salt poor diet with high fluids
	December 27	78 1		+	2 days before death Stuporous, taking no fluids
15012	December 5	106 1		0	On admission
	December 22	90 4		0	After salt poor diet with forced fluids
	January 20	103 7		0	Records inadequate
28049	February 8	89 2		(+)	
	February 11	80 4		(+)	Salt poor diet, high fluids Negative Cl balance
	February 16	86 9		+	Negative Cl balance
	February 25	87 4			Negative Cl balance
	March 1	87 2		+	Negative Cl balance
	March 4	93 0			Subcutaneous saline on March 2 and 3
	March 7	87 2			Deep stupor — Taking no food, fluids nor salt
	March 8	89 9			12 hours before death — Taking no food, fluids nor salt
35795		92 2	146 3	++	On admission
52843	October 11	99 8	146 3	+	
	October 20	93 9	142 2	+	Vomited until October 17 and took little food, fluids or salt

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foods was contemplated, but was not adopted Such diets would have been highly desirable from the standpoint of securing superior data, but, from the standpoint of therapy and the happiness of the experimental subjects, would have been less satisfactory than the diets actually given, which were chosen with attention to the tastes and caprices of the patients and with careful consideration of existing psychological and physiological disturbances of appetite, digestion and other functions

Examination of table 1 shows that in 25 out of 63 instances low serum Cl was observed in patients who had, during a preceding period, received little or no salt, either because they had been given salt poor diets or because, on account of coma, stupor or vomiting, they had been unwilling or unable to take diet or fluids Besides this in every one of the 16 examinations in which hypochloremia was found at the time of admission to hospital persistent vomiting had been an outstanding symptom In three other instances Cl balances had been distinctly negative In still another three, Cl was still low, but had risen from a previous lower level in response to the administration of sufficient salt to produce a positive balance Data are inadequate for the analysis of four determinations On three occasions bicarbonate had been given Twice edema appeared to explain the coexistence of hypochloremia and a positive Cl balance

This leaves only 7 out of 63 instances in which, while patients were in the hospital, reduction of Cl, which could not be explained on the basis of relative dietary deficiency, persisted

Vomiting, which was a prominent feature in 55 of the total 77 and in 48 of the 63 hypochloremic observations, offers the most obvious explanation for the deficits of Cl and base It was, however, entirely lacking on 7 of the 15 occasions when low Cl followed or was associated with insufficient salt intake

It has generally been held, with much experimental support, that it is impossible by limiting salt intake to reduce significantly the chloride concentration of the serum of normal individuals, even if high fluids are given unless, at the same time, Cl loss by extrarenal channels is augmented The normal kidneys appear to offer an effectual bar to chloride depletion Furthermore, if chloride loss by other channels is increased as, for instance, in pyloric obstruction,

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TABLE 2—*Continued*

Case number	Date	Serum Cl	Urine volume	Urine Cl		
	1924	*mM*	*cc*	*mM per liter*	*mM per day*	
29522	March 6	91 8	360	16	6	
	March 16		1,280	24	31	
	March 17	89 6	1,080	21	22	
	April 1	92 6	380	33	11	
	1925					
29267	November 26		2,520	41	10	
	November 27	96 4	2,800	40	11	
	November 30		1,270+	39	50+	
	December 1	95 3	1,770	42	74	
	December 5		950	164	156	
	December 6	96 2	520	263	137	
	1926					
	January 1		2,860	44	125	
	January 2	94 4				Involuntary
56247	January 17		1,560	18	27	
	January 18	94 7	1,500	30	44	
	January 24		1,500	24	36	
	January 25	92 5	1,560	19	29	
	January 31		1,390	21	29	
	February 1	87 0	1,390	21	29	
29635	April 17		1,970	18	26	
	April 18	88 8				
18496	June 2	95 0				
	1923					
22684	December 13	93 7	370	33	12	
	December 18		1,950	100	195	
	December 19	90 3	800	15	12	
	December 30		325	5	2	
	December 31	75 4	540	8	4	
	1924					
29796	April 7	93 7	580	30	17	
	1923					
18925	June 15	94 4				
	June 18			59		
	June 20	78 1		64		

urine Cl diminishes rapidly to vanish, finally, when serum Cl has fallen to a certain minimum level Ambard (4) claims that Cl disappears from the urine when its concentration in the serum drops below 96 milliequivalents (5 62 grams per liter) In a series of

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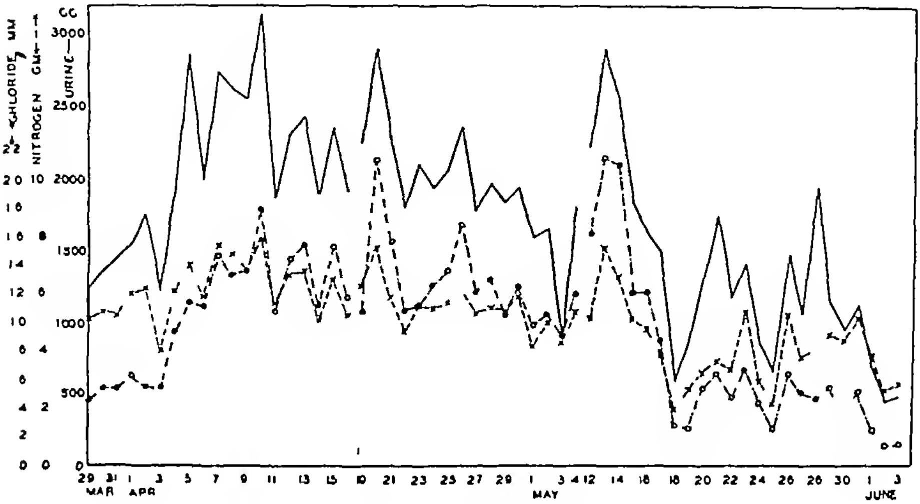

FIG 1 CASE 20921

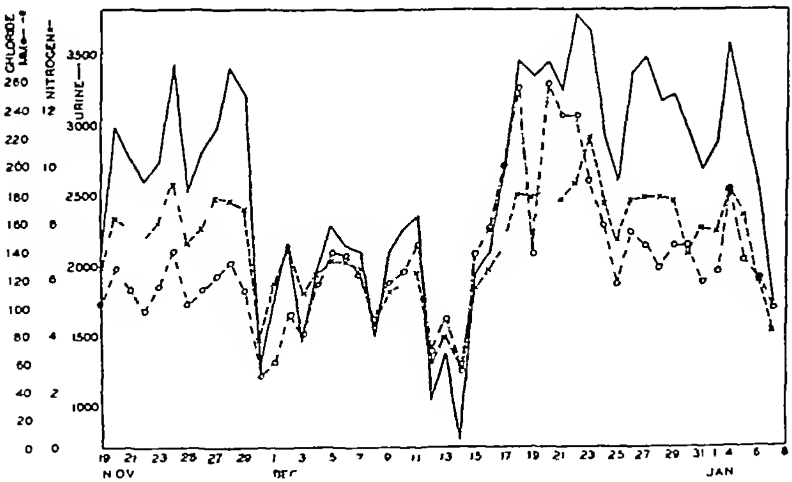

FIG 2 CASE 29267

solution of the same molecular concentration as blood serum This fixation of concentration is supposed to be exhibited in the excretion

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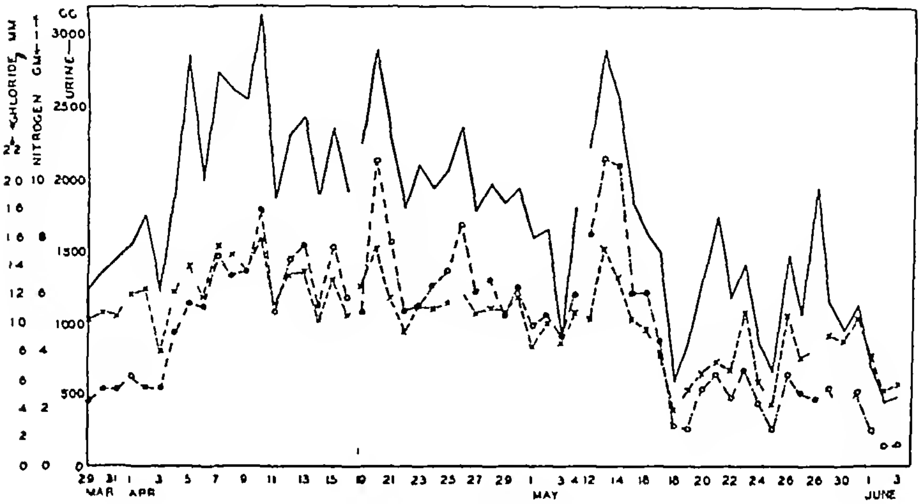

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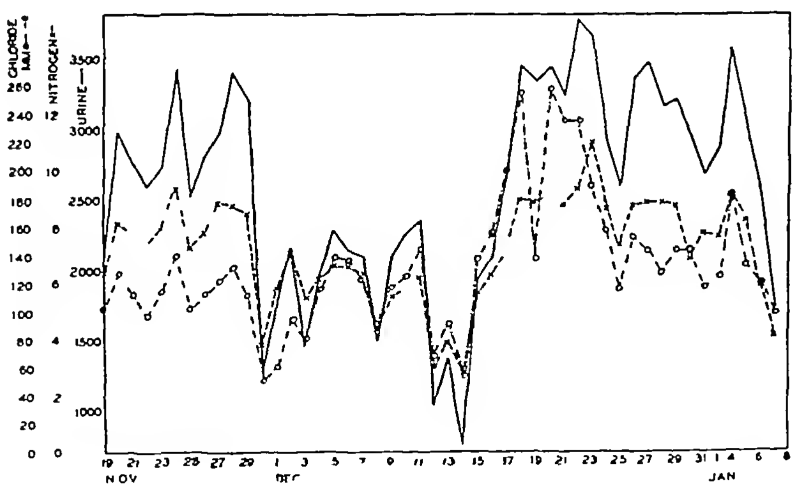

FIG 2 CASE 29267

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long periods, although it is relatively fixed over shorter intervals Comparison with the level of serum chloride also reveals no close relation with either concentration or total amount of chloride in urine To be sure both rise considerably when the serum chloride is pushed up by the administration of large amounts of chloride as, for example, in the middle period of figure 3 On the other hand at the end of the course of study of this case both total excretion and concentration were at almost the same level as they were at the beginning, although serum Cl had fallen from 100 5 to 91 6 mM

It is, apparently, possible to elevate the concentration of chloride in serum and in urine and to augment its excretion by the administration of sufficiently large amounts of salt On the other hand, water and chloride excretion seem to be more dependent upon one another than normal under any given conditions, as is evidenced by the rough parallelism between them in the charts Furthermore, chloride continues to be eliminated at a rather constant rate at levels of serum Cl that usually result in achloruria Finally, in no case studied did even the most vigorous administration of salt lead to the elimination of a urine of high salt concentration even if serum Cl was driven far above the normal level In fact only on two or three isolated occasions on single days in different patients did the urine chloride concentration equal that of the nearest serum observations In these instances it is quite possible that serum chlorides were higher at the time of passage of the concentrated urine than they had been when the blood was withdrawn for analysis

There is, then, an evident tendency to hyposthenuria and isosthenuria for Cl, although it is possible to cause considerable variation in the concentration of Cl below a certain level The data suggest that the limit of concentrating power is the concentration of Cl in the serum

If there is a definite hyposthenuric tendency, administration of either salt or water, within the capacity of the organism, should facilitate the excretion of the other If there is any tendency at normal or high levels of Cl for salt excretion to be accelerated and for diuresis to occur, it would seem advisable to adopt measures to promote such a process If, even at low levels of Cl ingestion and of serum chloride, excretion continues and is facilitated by water diuresis, administration

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usually far in excess of that in vomitus In another sense vomiting is by no means a negligible factor in the production of hypochloremia When vomiting seriously interferes with the ingestion of adequate amounts of food and fluids, the salt intake becomes of necessity limited and chloride wastage through the kidneys ensues as it does when a salt-poor diet is given

It is of some interest to note that hypochloremia does not have the same limiting influence on gastric Cl elimination as it does on urine chloride excretion Cl may be excreted in relatively high concentration in vomitus when the urine has become almost chloride free This is best illustrated by case 35805, tables 1 and 5 Studies of pyloric stenosis would lead us to expect these results In most of the observations deductions concerning the concentrating powers of the stomach can not be drawn because it is uncertain how much of the Cl recovered was derived directly from recently ingested food A few cases, especially 35805 and 56247 received nothing by mouth except occasionally salt-free carbohydrate fluids, all salt was given subcutaneously

Analysis of both vomitus and urine still failed to account for all the salt lost from the serum in some cases, so examination of feces was undertaken In most instances the amount of Cl in the stools was appreciable but not great and appeared to be due to the loss of urine during defecation, a frequently neglected factor that in these experiments has proved to be a source of large error It is surprising how few patients, especially among women, can control the vesical and anal sphincters independently with any consistent measure of success Case no 56247, table 4, however, does show a loss of Cl in the stools so large that it can not be explained as due to urine Whether similar leakage of chloride via the bowel is a common cause of salt loss in nephritics or only a peculiar anomaly of this individual remains to be determined when other subjects presenting similar conditions are observed It at least offers a possible explanation of some hitherto inexplicable chloride deficiencies

Low serum base

In general fluctuations of serum Cl are reflected in parallel variations of base, although there are exceptions to this rule, as has been indi-

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TABLE 3

Case no 29267

Date	Weight	Fluid		Nitrogen			Cl			Urine		Blood N P N	Serum	
		Intake	Urine	Intake	Urine		Intake	Urine		Base	B − Cl		Cl	Base
1925	*kgm*	*cc*	*cc.*	*grams*	*grams per liter*	*grams*	*mM*	*mM per liter*	*mM*	*mM*	*mM*	*mgm per 100 cc*	*mM*	*mM*
November 19	59 0	2,900	2,060	9 7	3 1	6 4	127	50	103			167	105 5	173 0
November 20		3,500	2,980	9 8	2 8	8 2	128	43	128	178	50			
November 21		3,100	2,740	9 4	2 8	7 8	118	41	112	178	66			
November 22		3,400	2,600	9 6	2 8	7 4	142	38	98	164	66			
November 23		2,800	2,720	9 3	2 9	8 0	169	42	114	177	63			
November 24	58 8	4,750	3,420	8 2	2 7	9 4	147	41	140	196	56	160		
November 25		3,700	2,520	8 1	2 9	7 3	118	40	102	136	34			
November 26		4,900	2,800	7 1	2 8	7 8	118	40	112	154	42			
November 27	59 0	3,850	2,960	7 1	3 0	8 9	118	41	121	181	60	168	96 4	132 9
November 28		3,900	3,400	7 4	2 6	8 8	113	39	131	175	44			
November 29	58 1	4,530	3,200	6 9	2 7	8 5	149	35	111	188	74			
November 30		3,950	1,270+	5 5	3 0	3 8+	309	39+	50+					
December 1		5,000	1,770	6 0	3 3	5 8	39	34	60	104	44	167	95 3	148 0
December 2		2,230	2,170	0	3 3	7 1	53	44	96	155	59			
December 3		4,180	1,470	0	3 7	5 5	212	54	80	118	38			
December 4		2,880	1,950	5 1	3 2	6 2	75	59	116	164	48			
December 5		3,720	2,290	3 3	2 9	6 6	272	61	139	190	51			
December 6		4,550	2,040	0	3 2	6 6	282	67	137	192	55	163	96 2	137 5
December 7		3,670	2,000	1 8	3 2	6 4	60	62	123	172	49			

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December 7		3,670	2,000	1 8	3 2	6 4	60	62	123	172	49			

TABLE 4

Case no 56247

Period	Days		Fluid		Nitrogen					Cl					Initial		
			Intake	Urine	Food	Urine	Stools	Vomit	Balance	Intake	Urine	Stools	Vomit	Balance	Weight	Blood N P N	Serum Cl
			cc.	*cc*	*grams*	*grams*	*grams*	*grams*	*grams*	*mM*	*mM*	*mM*	*mM*	*mM*	*kgm.*	*mgm per 100 cc*	*mM*
II	7	Total	16,130	11,530	56 6	53 0	21 6	0	−12 0	265	540	910	0	−1,185	61 6	77	99 2
		Daily	2,300	1,650	8 1	7 6	3 1	0	−2 6	38	77	130	0	−169			
III	7	Total	19,330	9,100	65 6	42 8	12 9	0	−9 9	327	253	503	3	−433	59 3	98	99 0
		Daily	2,760	1,300	9 4	6 1	1 8	0	−1 4	46	36	72	0	−62			
IV	7	Total	21,240	8,530	60 9	39 8	12 9	0	−8 2	301	320	503	0	−422	60 4	88	94 9
		Daily	3,030	1,220	8 7	5 7	1 8	0	−1 2	26	31	72	0	−60			
V	8	Total	28,280	14,630	12 4	42 2	3 7		−33 5	758	243	253	116	145	60 9	121	92 5
		Daily	3,540	1,830	1 6	5 3	0 5		−4 2	94	31	32	15	19			

TABLE 4

Case no 56247

Period	Days		Fluid		Nitrogen					Cl					Initial		
			Intake	Urine	Food	Urine	Stools	Vomit	Balance	Intake	Urine	Stools	Vomit	Balance	Weight	Blood N P N	Serum Cl
			cc.	*cc*	*grams*	*grams*	*grams*	*grams*	*grams*	*mM*	*mM*	*mM*	*mM*	*mM*	*kgm.*	*mgm per 100 cc*	*mM*
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		Daily	3,540	1,830	1 6	5 3	0 5		−4 2	94	31	32	15	19			

TABLE 5—*Continued*

Case number	Date	Urine			Vomit							Serum Cl
		Volume	Cl		Volume	Cl		Free acid		Total acid		
		cc	mM per liter	mM	cc	mM per liter	mM	mM per liter	mM	mM per liter	mM	mM
34802	October 9											91 6
	October 10				200	82	16	4	1	21	4	
					230	31	7	0	0	2	0	
	October 11				57	29	2	0	0	18	1	
					153	94	15	19	3	73	11	
					418	34	14	0	0	23	10	
	October 14				78	50	4	6	0	28	2	79 7
	October 15				255	72	18	0	0	22	6	
					125	46	6	0	0	22	3	
	October 19				200	79	16	9	2	38	8	
	October 21				73	98	7	0	0	45	3	
	October 22				136	89	12	0	0	24	3	
					160	123	20	0	0	50	8	82 8
	October 23				70	140	10	0	0	39	3	
					122	87	11	0	0	13	2	
	Total				2,277		158				64	
29267	December 1	1,700	42	73	260	50	13	0	0	41	11	95 3
	December 2	2,200	51	111	230	62	14	12	3	73	17	
	December 4	2,000	60	118	31	70	2	16	0	73	2	
	December 5	2,300	68	156	186	96	18	8	1	46	9	
	Total	8,200		458			47		4		39	
	December 6											96 2
56247	January 13	1,170	38	32			3					
	January 25	1,560	45	29	1,100+	45	41+					92 5
	January 26	980	34	34	1,400+	79	56+					
	January 27	1,470	45	31	290+	55	19+					
	Total	4,010		94	2,790+		116+					

combination with endogenous carbonic acid while excreting the Cl neutralized by ammonia In nephritis such adjustment is difficult, if not impossible Therefore, to restore complete normal equilibrium, it may be necessary to administer bicarbonate as well as chloride at times

de Wesselow (8) has suggested that vomiting is itself an adaptive

TABLE 5—*Continued*

Case number	Date	Urine			Vomit							Serum Cl
		Volume	Cl		Volume	Cl		Free acid		Total acid		
		cc	*mM per liter*	*mM*	*cc*	*mM per liter*	*mM*	*mM per liter*	*mM*	*mM per liter*	*mM*	*mM*
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be permeable to anions, peculiarities of distribution appear that suggest that such permeability is relative It is, apparently, conditioned by (*a*) certain acid patterns that are characteristic of individual tissues and (*b*) the need for readjustments in response to local endogenous acid production

Such considerations alone would make the estimation of the chloride content of the body, or even its changes, from corresponding serum concentrations exceedingly hazardous The data that have been presented dealing with salt balances indicate that, in general, increases in blood salt concentration, other things being equal, are associated with retention of salt Attempts to relate the two quantitatively have not been eminently successful Besides the incalculable distribution of Cl in body fluids and tissues, the proportions of these fluids and tissues themselves are constantly changing to increase the difficulty In certain studies that will be presented later attempts have been made to estimate gains or losses in tissue by means of the nitrogen balance and, employing these for the correction of weight changes, to determine by difference alterations of the water content of the body Similar methods applied to some of the cases of this series tend to show that the body water content in advanced nephritis is quite variable and that fluctuations in water content are attended by similar changes in salt balance

Although it is quite evident that blood water and tissue water are not always closely related, in the majority of instances anhydremia is attended by hemo-concentration Striking exceptions may be pointed out, usually in the presence of edema, when the blood may be inspissated while the tissues contain an excess of fluid Examples of this may be found in a diabetic case previously reported by the authors (9), and in one case of this series With the exception of such cases, however, in which hydrostatic factors may have played the chief part, the water content of the blood seems to reflect changes in the hydration of the body as a whole

Attention has already been called to the variability of serum proteins in this series of cases and to the probability that these variations are partly due to changes in blood water Simultaneous determinations of serum volume by the dye method of Keith, Rowntree and Geraghty (10), in case no 56247 have shown that this is the case The results

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CONCLUSIONS

Hypochloremia and deficiency of base in the serum in advanced nephritis seem to be the results of:

1 A tendency for both base and chloride to be excreted in the urine when serum Cl has fallen below the level which, in the normal individual determines achloruria

2 Vomiting, which attains its effect less by producing direct chloride loss than by interfering with salt intake

a The vomitus in uremia contains little free hydrochloric acid A considerable amount of the Cl in such vomitus exists in the form of BCl

b Although the concentration of Cl in vomitus remains high even in the face of advanced hypochloremia the total Cl loss by emesis is usually small compared with that in the urine

3 Considerable quantities of Cl may be lost in the feces in certain cases even if there is no diarrhea

There is no necessity of postulating any peculiar redistribution of chlorides in the body to explain the hypochloremia

The distribution of Cl is discussed as are the relations of changes in body water and salt content It is pointed out that hypochloremia and low serum base are usually attended by anhydremia and general dehydration

The therapeutic implications of these findings are discussed

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few leucocytes or red blood cells A year after discharge albuminuria persisted, but edema had not returned as long as he continued treatment His blood pressure was 164/88 on one occasion, at other times normal In 1924 he had become infected with syphilis and his Wassermann was found to be strongly positive

Case no 35628 (Protocol given at length in a previous paper (3)), a Polish male, aged 43, four months before admission, after tonsillitis, developed generalized subcutaneous edema, double hydrothorax and ascites His blood pressure was normal The urine contained much albumin, many casts, moderate numbers of leucocytes and variable numbers of red blood cells Early in his course in the hospital he had two attacks of sore throat with fever His edema did not subside until after tonsillectomy, March 17th

Case no 34854 (Protocol of first admission given at length in a previous paper (3)), a Polish male, aged 29, was admitted with generalized subcutaneous edema, double hydrothorax, ascites and splenic enlargement, which had first appeared two years earlier after an attack of polyarthritis and had been aggravated by frequent sore throats which had continued even after tonsillectomy His blood pressure was 155/95 on admission, but soon fell to normal His urine contained much albumin, many casts and leucocytes and variable numbers of red blood cells (sometimes gross blood) His course was marked by attacks of sore throat associated with fever and exaggeration of the hematuria He was discharged in August, but returned the next June, after a prolonged stay in another hospital, temporarily free from edema, but sick and emaciated After July 10th, symptoms and signs suggesting embolic phenomena appeared with increasing frequency September 19th and October 8th he had typical apopletic seizures and died shortly after the second

Autopsy revealed a massive cerebral hemorrhage, evidences of old and recent infarcts in several organs, a single, small fresh vegetation on the mitral valve, and large, swollen, kidneys that presented evidences of focal embolic lesions diffuse glomerular nephritis and tubular degenerative changes

Case 56883 An American male, aged 21, was admitted because of a profuse albuminuria that had developed after a severe attack of "grippe" five years earlier His blood pressure was normal The urine contained much albumin and moderate numbers of casts and leucocytes

Case no 50265 A Swiss male, aged 36, with tuberculosis of the upper lobe of the left lung and a chronic discharging right ear, developed edema of the lower extremities six months earlier His blood pressure was normal The urine contained large amounts of albumin and many casts, but no red blood cells nor leucocytes

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Bacteriological studies of the urine, blood and throat or other possible foci of infection were made in most cases Cultures of the urine proved sterile in cases 29122, 50265, 56883, 56577, 61090, 62246, 61711 and 34753 The urines of 50256, 56577 and 34753 were also repeatedly examined for tubercle bacilli but none were found, cultures and guinea pig inoculations were also negative Blood cultures from 34854 were repeatedly negative, although the urine cultures on several occasions yielded non-hemolytic streptococci Urine cultures from 35628, on two occasions recovered a Gram-negative, non-motile bacillus which produced no acid on most sugars and was not agglutinated by the patient's serum Cultures from the abscess of 56577 yielded staphylococci Throat cultures from 61090 revealed chiefly non-hemolytic, but some hemolytic streptococci In the case of 61711, hemolytic streptococci were obtained repeatedly from the throat during the acute infections, the same organisms were later recovered from the mastoid, and finally from the blood and the peritoneal cavity

Besides the examinations of the blood which are presented in the table, studies of nitrogen and chloride in food and urine were made on cases 35628, 34854 and 50265 Stools and vomitus of cases 61090, 62246, 61711 and 34753 were also examined for the same constituents The notes on chloride balance in the table are derived from these data, which will be presented in more detail in another paper

As a matter of routine all patients, as long as edema was evident, received diets which contained not more than 2 grams of Cl (as NaCl) daily Limitation of fluid was purposely practised only while edema was extreme Fluid intakes were, however, seldom large because, deprived of salt, patients lost their desire for water When edema could no longer be detected increasing measured amounts of salt were given, these were discontinued if evident retention of fluid ensued If rest, diet and salt regulation were not followed by diuresis, ammonium chloride, urea and sometimes other diuretic drugs were given

ANALYSIS OF RESULTS

The results of electrolyte studies with weights of patients and notes on edema and salt balance are presented in table 1

No attempt will be made in this discussion to differentiate the nephroses from the glomerular nephritides In the authors' opinion such a differentiation on a functional basis is impossible and on a clinical basis extremely difficult Only a classification on etiological grounds can be of great value At certain stages of the disease 29122, 31190, 50265, 56883, 56577, 61090, 62246, 61711 and 34753 presented the characteristics of nephrosis Of these 34753 proved to have a true amyloid nephrosis Case nos 50265 and 56577, with pulmonary tuberculosis and chronic osteomyelitis respectively, may well have the

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TABLE 1—*Continued*

Case number	Date	Weight	1 Serum total protein*	Albumin	Globulin	2 HCO_3	3 Cl	4 Inorganic P	5 Acid 1 + 2 + 3 + 4	6 Base	Undetermined acid 6–5	Blood non protein nitrogen	Phenolsulphonephthalein test	Edema	Cl balance	Diet NaCl†	Treatment‡
	1928	*kgm*	*m eq*	*m eq*	*m.eq*	*m eq*	*m eq*	*m eq*	*m eq*	*m eq*	*m eq*	*mgm per 100 cc*	*per cent*				
56577	March 23		13 5	7 8	5 6	26 3	103 6	2 3	145 7	150 2	4 5	27		±			
	1926																
34753	October 21	66 5	7 4			33 0	100 8	3 0	144 2	142 9	−1 3	31		+			
	October 29	66 5	7 9			30 2	101 2	3 0	142 3	141 1	−1 2	33		+		0	
	November 6	65 2	7 1			29 6	101 0	2 7	140 4	144 8	4 4	35	48	+		0	
	November 16	66 1	7 4			30 5	105 5	8 3**	151 7**	150 9	−0 8**	25		+		0	
	December 2	65 2	9 2			31 1	99 5	2 3	142 1	141 3	−0 8	30		+		0	
	December 9	66 8	8 5			30 9	104 8	3 1	147 3	155 9	8 6	27	50	+		0	
	December 18	64 0	8 5			30 6	102 4	10 0**	151 5**	146 0	−5 5**	10s††		+		0	
	December 23	63 4	8 6			25 2	109 7	2 8	146 3	144 9	−1 4	23		+		0	NH_4Cl
	1927																
	January 7	68 0	10 4			30 2	103 4	2 8	146 8	144 9	−1 9	23		+		0	
	February 16	57 8	8 5			28 9	104 4	2 2	144 0	142 0	−2 0	32		+			
	April 8	71 3	9 0			30 0	105 2	2 5	146 7	149 6	2 9	25		+			
	July 1		8 2	6 0	2 3	29 4	104 4	2 2	144 2	151 9	7 7	29		+			
	July 22	70 6	7 8	4 2	3 5	28 1	105 8					27		+			
	1928																
	January 13		7 2	3 4	3 8	23 1	107 8	2 7	140 8	155 8	15 0	56		+		+	Peritonitis
	February 4‡‡	73 0	7 5	3 7	3 8	16 3	103 4	4 4	131 6	142 3	10 7	85		+		+	
	February 8‡‡		8 8	4 5	4 3	14 7	96 4	6 9	126 8	141 2	14 4	155		0		+	
	February 10‡‡		8 6	5 6	3 1		89 0	11 1				238		0			
	February 12‡‡		5 6	3 7	1 9		88 0	12 2		152 8		301	Post-mortem pleural fluid				

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tionated estimation of the base combined with it is too large In the same studies, then, the estimated value for "undetermined acid" is correspondingly too small This offers an adequate explanation for most of the negative (base < total determined acid) values recorded Some of these (34854, December 6 and 34753, December 18), however, are so large that they can hardly be explained on this score Furthermore, similar negative values were found in two instances when proteins were fractionated, 61090, September 21 and 62246, November 15 (There is some reason to doubt the accuracy of the determinations on 31190, June 4 and 62246, February 7) It is hard to believe that the sum of acid equivalents in blood serum can ever exceed that of base, it is almost as hard to believe that the estimations of combining equivalents of acids other than protein can be greatly in error It is also worthy of note that similar negative values have not been found in a large number of observations of normal human subjects, and have been encountered extremely rarely in patients with other pathological conditions

On the whole organic acid concentration is seldom high and usually quite low High values seem to appear at certain stages of the disease in individual cases only, and may well be due not to the renal disease itself, but to some concomitant symptoms or conditions such as intercurrent infections or vomiting

Inorganic phosphate, with few exceptions, lay within the limits of normal variation It usually fell slightly as edema disappeared and patients improved Minor fluctuations can be observed following certain therapeutic measures, especially ammonium chloride The latter will be discussed elsewhere Occasionally decidedly high figures were obtained without any evident reason, notably in cases 34753, November 16 and December 18, and 61090, October 25 and 31 (The last two values in 34753 must be laid to the effects of peritonitis) So suddenly and unexpectedly do these high levels appear and disappear that one is inclined to ascribe them to technical errors Duplicates checked well and normal values were obtained from other patients on the same days The sera were separated so expeditiously and with such care that there is no reason to believe that phosphorus escaped from cells to serum In extensive studies of normal and diabetic sera no such high values were ever found In this series they

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Bicarbonate Reduction of bicarbonate, when it occurs, does not seem to be due to accumulation in the blood of abnormal acids Organic acid and phosphate are seldom elevated Bicarbonate deficit (acidosis) is usually associated with hyperchloremia, low base or both Because protein is low, bicarbonate is forced to yield less than it otherwise would to these factors and serious bicarbonate deficits are seldom observed except after ammonium chloride When Cl remains normal as in 34753 and 62246, bicarbonate is often high in spite of base deficiency, by virtue of the small base combining powers of the diminished protein

Base The outstanding feature of the total base values is their variability This is illustrated in figure 1 Of the 59 base determinations 35 lie either above or below the normal limits The distribution of these abnormal values is illuminating 29, or almost half of the total number of observations are low, while only 6 are high Certainly, in this series of cases, base deficiency is far more common than base excess The proportions of water to solids in several instances was directly determined The weight of solids, as was expected, tended to parallel the protein concentration[1] and was therefore, low This would seem to establish the fact that the total concentration of electrolytes per unit of water in the sera of these subjects was low, a condition which should cause the osmotic pressure to fall below the usual level (hypotonicity) Often enough this condition may have been produced or favored by the treatment, restriction of salt without purposeful restriction of fluids It was, however, found (in case 34753 for example) before treatment

The level of base bore no direct relation to that of any other serum component studied, nor was it associated with the concentration of non-protein nitrogen in the blood

DISCUSSION

Only one abnormal feature is characteristically and consistently encountered in the electrolyte picture in the sera of patients with the hydropigenous nephritides this is reduction of the concentration of protein, and especially the albumin fraction Furthermore, this is

[1] Presumably because of their large lipoid content, sera from these patients contained a larger quantity of solids in proportion to protein than was found in the sera of other patients

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the only change that can be related with any consistency to the occurrence of or tendency to edema Figure 2 shows that edema was almost invariably found when the total serum proteins were less than 4 per cent and never occurred when they exceeded 5 per cent Linder, Lundsgaard and Van Slyke (9) found a similar relation between tendency to edema and protein concentration This lends considerable support to the theory of Govaerts (10) and Schade and Claussen (11) They believe that protein deficiency, by reducing the colloid osmotic pressure of the serum, diminishes the force which ordinarily resists the tendency of hydrostatic pressure (blood pressure) to force fluid through the capillary walls into the tissues In the edematous nephritides the colloid osmotic pressure is reduced even more than the total serum protein concentration would indicate, because the osmotic pressure of a gram of albumin is, as Govaerts (12) has shown, much greater than that of a gram of globulin

Alterations of organic acid and phorphorus are rare and must play an unimportat part in the pathogenesis of edema and other symptoms

Bicarbonate also appears to occupy a rather insignificant, if helpful position Its behavior seems to illustrate beautifully what Gamble (13) has called its "mendicant position" It effaces itself as far as possible when there is too little base to completely satisfy inflated Cl, thankfully accepts what base the weakened proteins can no longer hold It is hard to believe that it is acting more than a helpful secondary rôle, fitting in where it may prove useful

Base has been found to be quite variable, sometimes above and sometimes below the normal limits In this series it was low in about one-half the determinations, high in only about one-tenth With the reasonable assumption that base is distributed in approximately uniform concentration throughout the fluids of the body, the frequent occurrence of base deficit is a cogent argument against the generally accepted theory that water accumulations in nephritic edema are entirely secondary to retention of sodium Reductions of serum base are, perhaps, more frequent in the studies here reported because a more purposeful effort was made to restrict salt in the diet than to limit the fluid intake However, low base concentrations were found in the sera of some patients before treatment was instituted

Serum base excess was observed especially during the earlier part of the hospital course of patients 35628 and 34854 At these times both

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the base changes here reported For the latter, alterations of sodium concentration must be chiefly responsible In this case repositories in which it may be retained are presumably extracellular,—i e , the edema transudates themselves Examinations of such transudates by others (15) and in case 61090 have invariably failed to reveal base concentrations higher in relation to those of the serum than would be anticipated on the basis of current theories of osmotic equilibrium Cl distribution is not so uniform (16), in two instances in the present investigation (61711 and 61090) the chloride concentration of transudates proved far higher than that of serum

In about one-third of the determinations the concentration of Cl was distinctly above the normal limits of variation, while hypochloremia was never observed This again is hard to explain on the theory that it is the basic ion Na^+ and not the acid Cl^- which is chiefly retained by patients with nephritic edema The chloride excess can not be looked upon merely as a compensatory reaction against protein deficit because it is sometimes so large (35628, January 13, 34854, October 16, 23, 28, November 6) that, with base normal or high, it makes up for the protein deficit and forces a recession of bicarbonate as well This would indicate that in the hydropigenous nephritides the Cl^- ion is usually excreted with the greatest difficulty [2] Nor is there any direct or indirect evidence of importance to prove that this is not the case Hyperchloremia has been found frequently by other observers (16, 17), high base rarely (14, 16, 17)

Changes in the concentration of the inorganic electrolytes can not be directly connected with the presence or absence or degree of edema This is clearly shown in figures 1 and 2 Extremely distorted electrolyte patterns are less often noted in the absence of edema, but the number of blood studies on non-edematous patients are, for obvious reasons, too few to permit valid comparison Distinctly abnormal electrolyte pictures involving disturbances of base, Cl and HCO_3 were certainly encountered when no edema could be detected Due consideration must, of course, be given to the fact that absence of edema was produced and maintained in most instances only by contin-

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nous tendency was at its worst, the production of extreme hyperchloremia and consequent acidosis was entirely ineffectual as a diuretic measure (34854, November 13 to 18, 34753, December 18 to 23, 61090, July 6 to 14) Salt poor diets in which both base and Cl were presumably low were more often followed by a fall of serum base than reduction of serum chloride All these results indicate that the Cl ion is excreted with extreme difficulty

Gamble (17) has suggested that the hyperchloremia is a reaction which promotes diuresis in these cases With this point of view the authors agree, but not with the apparent implication that it is a favorable adaptive reaction It is merely the direct result of failure to excrete Cl When this failure produces a sufficiently unbalanced electrolyte pattern diuresis results Diuresis may be induced by exaggerating the imbalance by giving ammonia chloride

By the same reasoning one would expect bicarbonate to favor retention of water If there is a specific excess of Cl or any other acid ion in the blood the administration of bicarbonate is equivalent to giving so much base The bicarbonate ion is excreted by the lungs, leaving the base to combine with the Cl This is, of course, a step towards the restoration of a normal electrolyte picture and must, therefore, remove the stress which was forcing diuresis

Transferring emphasis from sodium to chloride and water alters current therapy but little Restriction of salt remains the most practical routine procedure Diets poor in Cl are also poor in base Without salt the desire to take fluids diminishes, therefore the restriction of salt results in fluid limitation without distressing the patient

SUMMARY

1 The concentration of base and the most important acids (protein, bicarbonate, chloride and inorganic phosphate) in the serum, together with the nitrogen and chloride metabolism of patients with nephrosis and nephrotic types of chronic glomerular nephritis have been determined

2 Neither the level of proteins in the serum nor the electrolyte pattern permits differentiation between nephrosis and the nephrotic type of chronic glomerular nephritis

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provement clinically on the other, it seemed desirable to study further the creatine-creatinine metabolism in this disease as influenced by the administration of iodine Furthermore, the intimate association of creatine and creatinine with muscle function and the important and striking symptom of muscular weakness in this disease add interest to the observation we desire to report

EXPERIMENTAL

Cases of exophthalmic goiter were studied in a specially organized metabolism ward in order to insure proper dietary control and accurate collection of urinary specimens The diets employed were creatine-free with a caloric value equivalent to 100 per cent above the actually determined basal requirement The protein was fixed between 1 and 1½ grams per kilogram, the carbohydrate and fat distributed according to the individual preferences of the subject Invariably the carbohydrates were more freely taken than the fats Such a diet in our experience has established nitrogen equilibrium or a positive nitrogen balance within three or four days After a period of three days to a week iodine was administered as Lugol's solution in 1 to 3 cc amounts daily, in practically all instances as part of the preparation for partial thyroidectomy Creatine and creatinine were determined by the usual Folin method All specimens of urine were examined for ketone bodies before the determinations were made At the outset during the winter 1925–1926 uric acid and nitrogen balances were determined Later these observations were discontinued for reasons given later

Eight of the cases reported in this paper were studied by D A C in the Lane and Stanford University Hospital in San Francisco during the winter of 1927 and 1928 Some of these patients received iodine in the form of sodium iodide either alone or in association with Lugol's solution

RESULTS

For convenience in discussion the 43 cases studied are divided into two groups and arranged in order of the elevation of the basal metabolic rate in tables 1 and 2 The first group, table 1, includes the cases quite generally recognized as true exophthalmic goiter, and the second group in table 2 the subjects, as a rule older, without exophthalmos

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TABLE 1

Exophthalmic goiter *Group I*

Cases arranged in order of the initial basal metabolic rate

Case number	Hospital record number	Sex	Age	Weight	Basal metabolic rate above normal: Before Lugol's	Basal metabolic rate above normal: After Lugol's	Creatine: Before Lugol's	Creatine: After Lugol's	Creatinine: Before Lugol's	Creatinine: After Lugol's	Creatinine coefficient	Days before effect	Remarks
				kgm	*per cent*	*per cent*	*grams*	*grams*	*grams*	*grams*			
1	67755	F	31	62	90	48	0.58	0.00	0.60	0.53	10	7	
2*	169712	M	36	55	82	26	1.51	0.09	1.15	0.91	21	3	
3*	141738	M	35	49	79	32	1.08	0.05	1.03	0.75	21	7	
4	71191	F	17	46	79	62	0.25	0.00	0.40	0.45	9	8	
5	70682	F	22	57	71	15	0.65	0.03	0.60	0.60	11	6	
6	67955	F	38	53	65	15	0.43	0.00	0.80	0.90	15	4	
7	67911	F	31	59	65	15	0.50	0.00	0.60	0.70	10	3	
8*	172491	F	21	57	62	30	0.40	0.10	0.80	0.80	14	7	
9	65916	M	37	50	62	23	0.20	0.00	0.70	0.70	14	3	Colored
10	67444	F	21	63	60	15	0.70	0.05	0.90	0.80	14	3	
11*	171003	F	26	52	58	16	1.00	0.30	0.95	0.50	18	5	
12	70353	F	32	59	58	23	0.59	0.05	0.90	0.80	15	6	
13	71150	M	42	62	56	29	0.40	0.00	0.60	0.40	10	3	Colored
14	68592	F	26	36	55	30	0.55	0.03	0.60	0.60	17	3	Colored
15	65566	F	27	43	55	17	0.50	0.02	0.70	0.70	16	3	The creatine excretion was quite irregular in this case until after iodine was started
16	68083	F	29	68	55	23	0.65	0.03	0.60	0.60	9	4	Considerable difficulty was experienced in collecting complete specimens, the amounts reported are taken from days when the specimens were complete

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Case number	Hospital record number	Sex	Age	Weight	Basal metabolic rate above normal		Creatine		Creatinine		Creatinine coefficient	Days before effect	Remarks
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3*	141738	M	35	49	79	32	1 08	0 05	1 03	0 75	21	7	
4	71191	F	17	46	79	62	0 25	0 00	0 40	0 45	9	8	
5	70682	F	22	57	71	15	0 65	0 03	0 60	0 60	11	6	
6	67955	F	38	53	65	15	0 43	0 00	0 80	0 90	15	4	
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TABLE 2

Toxic adenoma Group II

Case number	Hospital record number	Sex	Age	Weight	Basal metabolic rate above normal		Creatine		Creatinine		Creatinine coefficient	Days before effect	Remarks
					Before Lugol's	After Lugol's	Before Lugol's	After Lugol's	Before Lugol's	After Lugol's			
				kgm	*per cent*	*per cent*	*grams*	*grams*	*grams*	*grams*			
1	66857	F	54	50	60	67	0 00	0 00	0 30	0 30	?		Case unsatisfactory from metabolic standpoint Included to show there was no urinary creatine
2*	167578	F	58	45	47	25	0 18	0 05	0 60	0 60	13	?	Creatine had decreased from 0 50 gram creatine before iodine was excreted
3	68778	F	45	56	40	0	0 05	0 50	0 70	0 70	13	?	Patient received only 4 cc Lugol's altogether in first ten days of experiment. The creatinuria increased thereafter
4	67195	F	51	60	40	35	0 10	0 05	0 60	0 60	10		This patient had 2 cc of Lugol's for 16 consecutive days without effect on general condition
5	70254	F	45	56	37	37	0 50	0 00	0 80	0 80	14	7	
6	67265	M	59	52	35	25	0 05	0 05	0 81	0 80	15		
7	67620	F	41	56	30	15	0 20	0 00	0 90	0 89	16	?	
8	71141	F	40	69	25	21	0 15	0 05	0 95	0 90	14	?	Seventeen days of iodine administration with only slight effect
9	54558	F	37	52	22	22	0 20	0 05	0 70	0 80	13	?	Creatinine was very irregular during course and probably due to incomplete specimens in part although this was never definitely established
10*	170541	F	38	60	18	14	0 40	0 05	0 76	0 75	13	5?	
11	69950	F	34	62	20	8	0 05	0 03	0 90	0 90	15		

* Cases observed at Lane and Stanford University Hospitals, San Francisco, by D A C

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Toxic adenoma Group II

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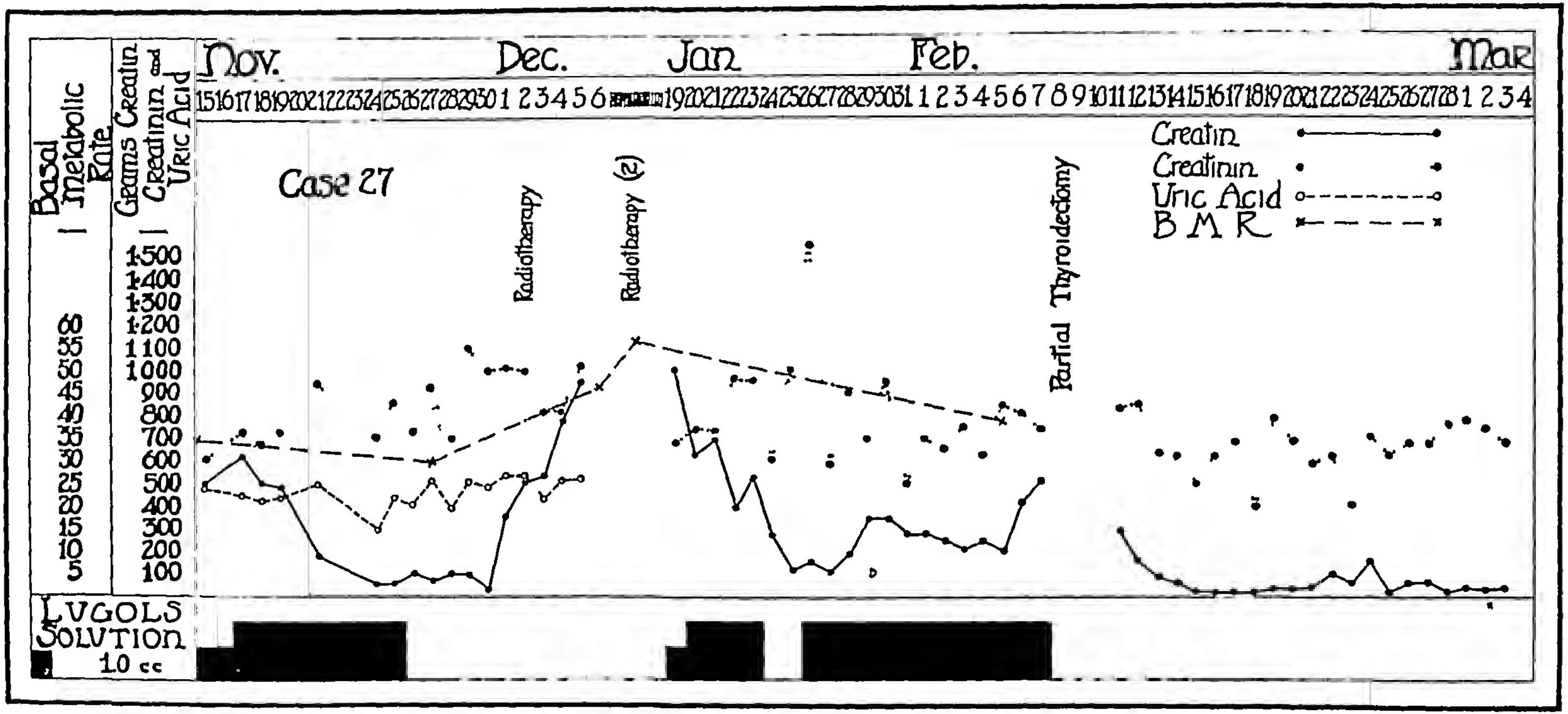

Chart 1 Case 27 Between December 6 and January 7 the Patient Received 2 cc Lugol's Solution Daily Except One Week Before the X-ray Treatment on December 24

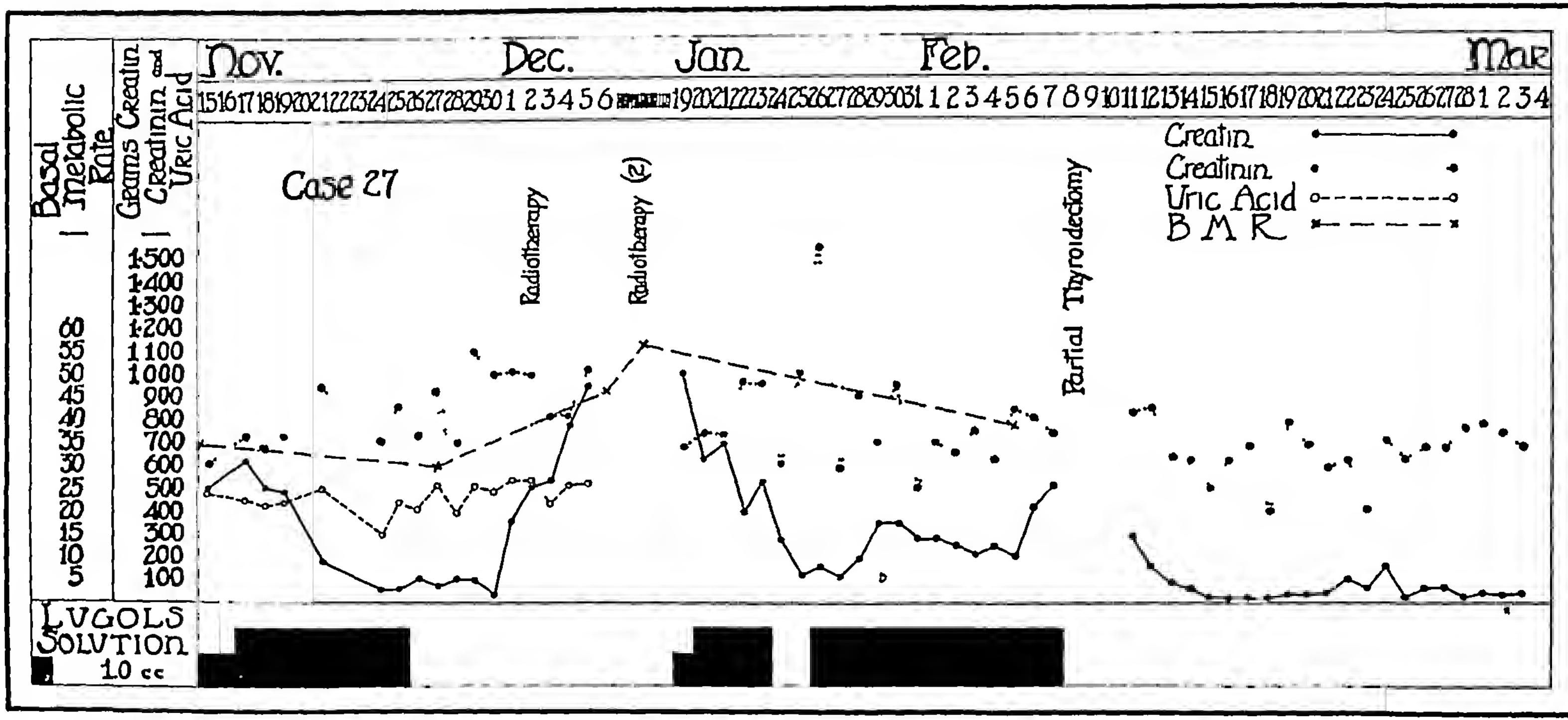

Chart 1 Case 27 Between December 6 and January 7 the Patient Received 2 cc Lugol's Solution Daily Except One Week Before the X-ray Treatment on December 24

from the urine Most of the clinical symptoms and metabolic disturbances in this disease are attributed to an increased amount of the active principle, thyroxine, circulating in the body The evidence for such a hypothesis is considerable Feeding thyroid gland or thyroxine to normal individuals and animals reproduces the symptoms and metabolic changes observed in the disease with the exception of exophthalmos In our experiments we were able to bring the subjects ill with exophthalmic goiter into nitrogen equilibrium without influencing greatly the creatinuria which is interesting in connection with Benedicts and Osterberg's (5) experiments with phlorizinized dogs which were given sufficient amounts of creatine-free protein to abolish the negative nitrogen balance without diminishing the excretion of creatine Following the administration of iodine there resulted a rapid diminution of the creatine in the urine to merely traces In a few instances this occurred without reduction of the basal metabolism, also a few cases with high basal rates excreted very little creatine with or without iodine As the latter phenomenon occurred most frequently in the group designated as "toxic adenomas" the question arises whether the pathological process in these cases differs in any way from the patients classified as exophthalmic goiter There is insufficient evidence at present to answer this question Certain it is that in those cases of hyperthyroidism with significant amounts of creatine in the urine there is marked diminution in the creatinuria following the intake of iodine It is difficult to separate this fact from the beneficial effect of iodine in general Marine suggests that the histological change in the hyperplastic thyroid gland brought about by iodine resulting as it does in distending the acini with colloid material, impairs the circulation in the vascular and lymphatic systems thereby preventing the escape of thyroxine into the general circulation This view would seem to be consistent with the evidence available at present Such being the case it would appear that thyroxine in abnormal amounts is directly associated with the appearance of creatine in the urine In support of this conception is the fact that both in men (6) and animals (7) creatinuria is produced by feeding either the thyroid gland or the actual principle Sturgis and associates (8) showed that the increased basal metabolism produced in rabbits by feeding thyroid extract was not lowered by the

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THE VITAMIN B CONTENT OF CANCER

By HENRY JACKSON, Jr., and CLEMENT L KRANTZ

(*From the Medical Service of the Collis P Huntington Memorial Hospital of Harvard University and the Thorndike Memorial Laboratory, Boston City Hospital*)

(Received for publication September 17, 1928)

Burrows (1) has been led to believe that cancer may be due to a local excess of vitamin B in the tissue and he and his co worker Jorstad bring forward some evidence that the Jensen rat sarcoma does actually contain an abnormally great amount of this accessory food substance (2) (3) They fed young rats a basic diet free from vitamin B to which were added ten grams Jensen rat sarcoma and from the growth curves obtained on this diet they conclude that cancerous tissue contains an abnormally great amount of vitamin B No normal resting organ was, however, directly contrasted with the malignant tissue, so we are left in doubt as to the exact quantitative differences in vitamin B content between normal and neoplastic tissue If cancer really be due to, or associated with, an increase of vitamin B, then actively growing neoplastic tissue should, as Burrows claims, contain more of this accessory food factor than normal tissue Experiments were therefore devised to check the results of Burrows and Jorstad as the matter is not without both theoretical and practical importance

Young white rats were placed on a basic diet containing

	per cent
Casein	18
Starch	54
Butter fat	24
Salt mixture	4

The salt mixture was that described by Osborne and Mendel (4) All ingredients were free from vitamin B Each rat was kept in a separate cage and adequate precautions were taken against the consumption of feces Tap water was given freely at all times Each rat was weighed every two days. The basic vitamin B free diet was renewed daily In addition to the basic diet each rat received in a separate

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Ten rats were fed human cancer, twelve were fed mouse cancer, six normal mouse liver, and four were placed on pure diets without addition of tissue (chart 1)

An examination of chart 1 shows that even 500 mgm dried human cancer per diem was insufficient to produce adequate growth After a

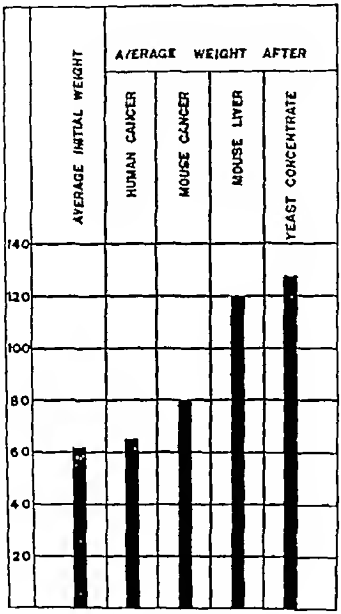

CHART 2 AVERAGE WEIGHTS AT THE BEGINNING OF THE EXPERIMENT AND AT THE END OF THE FEEDING PERIODS ON VARIOUS DIETS

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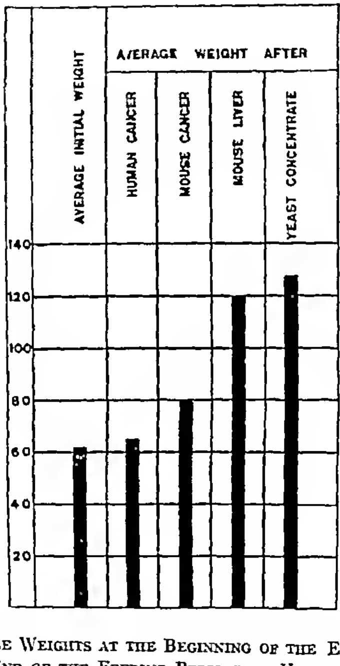

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STUDIES ON DIGITALIS IN AMBULATORY CARDIAC PATIENTS

II The Elimination of Digitalis in Man

By HARRY GOLD and ARTHUR C DeGRAFF

(From the Third Medical (New York University) Division of Bellevue Hospital and Department of Pharmacology of Cornell University Medical College)

(Received for publication September 14, 1928)

A study of the rate of elimination of digitalis in normal animals in terms of persistence of action was published by one of us (1) in 1923 The curves invariably show that after a single large injection, elimination is very rapid at first and then slower, i.e , as the quantity of digitalis in the body diminishes, that eliminated daily also diminishes This was demonstrated in another way as seen from the following example taken from that paper each of several animals received a single intravenous injection of 75 per cent of the average fatal dose of a given tincture of digitalis In 24 hours, the average quantity eliminated was 45 per cent of a fatal dose. If the capacity for elimination of the drug could be expressed as a fixed quantity per day—45 per cent of a fatal dose for this specimen—an animal receiving a daily intravenous injection of 50 per cent of a fatal dose of this tincture would require about 20 such daily doses to cause death, and an animal receiving a daily injection of 25 per cent of a fatal dose of this specimen would never accumulate sufficient digitalis in the body to cause death As a matter of fact, two animals that had received daily injections of 50 per cent of a fatal dose of this tincture died after the fourth and fifth dose, respectively, and two animals that had received daily injections of 25 per cent of a fatal dose died after the tenth and eleventh injection respectively The conclusion necessarily follows that the amount of digitalis eliminated daily depends upon the amount of the drug in the body, and that in all probability, only a percentage of that present can be eliminated in a unit of time

The curve of digitalis elimination is rendered complex by the presence

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The studies have been carried out upon ambulatory cardiac patients with auricular fibrillation, because in these the onset and disappearance of digitalis effects can be established with greater precision The type of medical and social service organization of this clinic[1] and the personal contact established between the patients and the staff, have made it possible to carry out observations over long periods of time with results as reliable, within limits, as those carried out on a hospital ward in this type of work. Patients who could not be depended upon to comply strictly with orders were excluded from the study Digitalis was employed in a manner similar to that described in a previous paper (6) Compressed tablets of dried digitalis leaf standardized by the cat unit method, were dispensed to the patients and the daily amount ordered to be taken in a single dose.

The ventricular rate was used to indicate the intensity of digitalis action and this was particularly satisfactory in that group of patients who are in this respect very sensitive to the drug, in whom marked changes in the ventricular rate occur readily when the drug is given or withheld In all instances the work and exercise during a given period were inquired about so as to exclude those cases in which it could not be stated with a fair degree of certainty that there was neither more exertion nor more rest to account for the changes in the rate attributed to the withdrawal or administration of digitalis The apex rate was counted by the stethoscope under fairly uniform conditions with the patient sitting or lying after a period of rest With these precautions, the occasional variability is far less striking than the general uniformity

[1] The Adult Cardiac Clinic of Bellevue Hospital

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Patient E P (chart 1) appeared at the clinic with a ventricular rate of 164, he had never had any digitalis He was permitted to go one week longer without the drug and the rate remained unchanged He was then given 0 2 gram daily of specimen "A" The rate gradually decreased, reached a level of about 80 by the third week, and remained constant during a subsequent period of observation of six weeks during which the same dose was taken Several months later, this patient was under the influence of digitalis and the ventricular rate was 64 The drug was withheld for a period of three weeks and the ventricular rate increased to 136 He was then given 0 2 gram daily of specimen "D" The ventricular rate again diminished gradually and reached a level of about 80, at which it remained for several weeks with the same daily dose of the drug This was repeated at a subsequent time with specimen "C"

Since progressively increasing intensity of the digitalis effect mentioned (depression of conduction) during the administration of a fixed daily dose of the drug is taken as evidence that the patient is receiving more digitalis than he is eliminating, it must be assumed that when this patient had no digitalis in the body, he was incapable of eliminating the 0 2 gram that was given daily, but after he had accumulated a certain portion of the 4 2 grams that had been given in a period of twenty-one days, he now was eliminating 0 2 gram daily

It is also interesting to note that the curves are essentially similar with specimens "A" and "D" which are very similar in activity, the former 79 mgm, the latter 87 mgm to the cat unit With specimen "C" it took more time to accumulate sufficient digitalis to produce the results as might have been anticipated from the fact that it was a poor specimen with an activity of 140 mgm to the cat unit

In patient J R (chart 2), after digitalis had been given for several months, the drug was withheld and the ventricular rate gradually increased during a period of twelve weeks to 120 The patient then received 0 2 gram daily of specimen "D" and the rate gradually diminished until it reached a level that was maintained for several weeks The dose was increased to 0 25 gram daily for fourteen weeks (98 doses) and the rate remained unchanged This indicates that a patient who was able to eliminate 0 25 gram daily after considerable digitalis had accumulated, was unable to eliminate even 0 2 gram daily

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TABLE 1

Showing the clinical classification of the patients used for the tests that are summarized in table 2

Number of patient	Sex	Age	Weight	Diagnosis: Etiological	Diagnosis: Anatomical	Functional classification*
			kgm.			
994	M	27	65 9	Rheumatic	Enlarged heart, mitral stenosis and insufficiency aortic stenosis and insufficiency	II-a
1261	M	39	70 9	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II b
65	M	56	66 3	Rheumatic	Enlarged heart, mitral stenosis and insufficiency, aortic stenosis and insufficiency	III
1119	M	58	100	Unknown	Enlarged heart	II b
1254	M	48	67 2	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II b
1369	M	58	98 6	Arteriosclerotic	Enlarged heart	II-b
1388	M	67	60 0	Arteriosclerotic	Enlarged heart	II b
1715	F	51	50 0	Arteriosclerotic	Enlarged heart	II-b
124	F	35	63 6	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II b
594	F	58	61 8	Arteriosclerotic	Enlarged heart	II b
1768	M	35	61 3	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II b
1181	M	54	62 2	Unknown	Enlarged heart	II b
948	M	18	40 9	Rheumatic	Enlarged heart, mitral stenosis and insufficiency, adhesive pericarditis	II b
1519	F	38	70 0	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II-b
1201	M	46	70 4	Unknown	Enlarged heart	II-a
629	M	51	71 3	Unknown	Enlarged heart, mitral stenosis and insufficiency	II-a
1848	F	36	60 0	Rheumatic	Enlarged heart, mitral stenosis and insufficiency	II b
1858	F	38	60 0	Unknown	Enlarged heart	II b
1728	F	60	83 6	Unknown	Enlarged heart	II b
679	M	32	55 9	Unknown	Enlarged heart, mitral stenosis and insufficiency	II b
1892	F	36	52 7	Unknown	Enlarged heart	II b
1855	F	41	90 9	Unknown	Enlarged heart mitral stenosis and insufficiency	II b
1615	M	67	86 3	Arteriosclerotic	Enlarged heart, aortitis	II-a

* (II a) able to carry on slightly diminished physical activity (II b) able to carry on greatly diminished physical activity (III) symptoms of heart failure at rest

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* (II a) able to carry on slightly diminished physical activity (II b) able to carry on greatly diminished physical activity (III) symptoms of heart failure at rest

TABLE 2—*Continued*

Number of patient	Number of test and specimen of digitalis	Daily dose	Number of days	Ventricular rate
		grams		
56	1 A	0	14	126
		0 2	7	84
		0 2	14	86
		0 25	7	84
		0 25	14	84
		0 25	14	78
		0 25	14	80
		0 25	14	82
		0 4	14	70
	2 C	0	7	96
		0 2	21	72
		0 2	28	66
		0 2	28	66
		0 2	28	66
		0 2	28	64
		0 2	28	66
	3-E	0	21	100
		0 13	28	82
		0 13	14	82
		0 13	21	80
		0 13	21	78
	4-E	0	28	120
		0 2	14	92
		0 13	21	74
		0 13	21	76
		0 13	14	84
		0 13	28	90
1119	1 C	0	14	112
		0 2	7	90
		0 2	7	78
		0 2	7	74
		0 2	14	74
		0 2	21	72
		0 13	14	74
		0 13	21	70
	2 D	0	35	130
		0 2	7	104
		0 2	14	94
		0 2	28	78
		0 2	28	88
		0 2	28	80
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		0 2	28	66
		0 2	28	66
		0 2	28	64
		0 2	28	66
	3-E	0	21	100
		0 13	28	82
		0 13	14	82
		0 13	21	80
		0 13	21	78
	4-E	0	28	120
		0 2	14	92
		0 13	21	74
		0 13	21	76
		0 13	14	84
		0 13	28	90
1119	1 C	0	14	112
		0 2	7	90
		0 2	7	78
		0 2	7	74
		0 2	14	74
		0 2	21	72
		0 13	14	74
		0 13	21	70
	2 D	0	35	130
		0 2	7	104
		0 2	14	94
		0 2	28	78
		0 2	28	88
		0 2	28	80
		0 2	28	88

TABLE 2—*Continued*

Number of patient	Number of test and specimen of digitalis	Daily dose	Number of days	Ventricular rate
		grams		
1768	1 E	0	77	120
		0 16	7	80
		0 16	7	80
		0 16	7	78
		0 16	3	
		0	4	78
		0	14	78
		0 16	14	78
1181	1-C	0	35	92
		0 2	14	66
		0 2	14	56
		0 2	21	68
		0 2	21	58
	2 D	0	42	100
		0 2	14	54
		0 2	14	68
		0 2	21	60
		0 2	21	58
948	1 A	0	months	200
		0 2	7	98
		0 13	7	96
		0 2	7	70
		0 2	7	86
		0 2	7	76
		0 2	7	80
		0 2	7	76
1519	1 E	0	7	120
		0 13	14	92
		0 13	21	100
		0 13	14	82
		0 2	14	84
		0 2	7	82
		0 2	7	84
		0 2	28	82
1201	1 D	0	133	160
		0 25	7	88
		0 2	14	78
		0 2	21	64
		0 2	7	66
		0 2	14	65

TABLE 2—*Continued*

Number of patient	Number of test and specimen of digitalis	Daily dose	Number of days	Ventricular rate
		grams		
1768	1 E	0	77	120
		0 16	7	80
		0 16	7	80
		0 16	7	78
		0 16	3	
		0	4	78
		0	14	78
		0 16	14	78
1181	1-C	0	35	92
		0 2	14	66
		0 2	14	56
		0 2	21	68
		0 2	21	58
	2 D	0	42	100
		0 2	14	54
		0 2	14	68
		0 2	21	60
		0 2	21	58
948	1 A	0	months	200
		0 2	7	98
		0 13	7	96
		0 2	7	70
		0 2	7	86
		0 2	7	76
		0 2	7	80
		0 2	7	76
1519	1 E	0	7	120
		0 13	14	92
		0 13	21	100
		0 13	14	82
		0 2	14	84
		0 2	7	82
		0 2	7	84
		0 2	28	82
1201	1 D	0	133	160
		0 25	7	88
		0 2	14	78
		0 2	21	64
		0 2	7	66
		0 2	14	65

TABLE 2—*Concluded*

Number of patient	Number of test and specimen of digitalis	Daily dose	Number of days	Ventricular rate
		grams		
679	3-F	—	—	120
		0 2	7	102
		0 2	7	94
		0 2	21	103
		0 3	14	86
		0 3	14	72
		0 3	21	64
		0 3	21	80
		0 3	21	76
		0 3	21	80
		0 3	21	78
1892	1 F	Tincture taken occasionally		132
		0 2	7	100
		0 2	7	81
		0 2	7	86
		0 2	7	86
1855	1 F	0	14	100
		0 1	7	83
		0 1	7	71
		0 1	7	76
		0 1	7	67
		0 1	21	70
		0 1	21	62
		0 1	21	57
		0 1	21	75
1615	1 F	0 2	294	72†
		0	7	72
		0	14	106
		0	7	110
		0	7	99
		0 13*	7	126
		0 2	7	106
		0 2	14	86
		0 2	21	68
		0 2	14	76
		0 2	21	74
		0 2	21	74

* Specimen E

† Average of 11 records.

TABLE 2—*Concluded*

Number of patient	Number of test and specimen of digitalis	Daily dose	Number of days	Ventricular rate
		grams		
679	3-F	—	—	120
		0 2	7	102
		0 2	7	94
		0 2	21	103
		0 3	14	86
		0 3	14	72
		0 3	21	64
		0 3	21	80
		0 3	21	76
		0 3	21	80
		0 3	21	78
1892	1 F	Tincture taken occasionally		132
		0 2	7	100
		0 2	7	81
		0 2	7	86
		0 2	7	86
1855	1 F	0	14	100
		0 1	7	83
		0 1	7	71
		0 1	7	76
		0 1	7	67
		0 1	21	70
		0 1	21	62
		0 1	21	57
		0 1	21	75
1615	1 F	0 2	294	72†
		0	7	72
		0	14	106
		0	7	110
		0	7	99
		0 13*	7	126
		0 2	7	106
		0 2	14	86
		0 2	21	68
		0 2	14	76
		0 2	21	74
		0 2	21	74

* Specimen E
† Average of 11 records.

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